REMARKS

After entry of this amendment, claims 1, 3-33 and 35-45 are pending. Claims 2 and 34 are cancelled; claims 1, 3-6, 32-33 and 35-37 are amended.

35 U.S.C. § 112 Rejections

Reconsideration of the rejection of claims 1, 7-30, 33 and 37-45 under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement is respectfully requested. Claims 1 and 33 are amended to include a chemical structure, which describes the methionine or methionine-like moiety. Accordingly, with the claim amendments, claims 1, 7-30, 33 and 37-45 satisfy the written description requirement.

Further, reconsideration is respectfully requested of the rejection of claims 1-45 under 35 U.S.C. § 112, first paragraph as failing to comply with the enablement requirement. As explained below, applicant respectfully maintains that the pending claims are fully enabled. In any event, it is believed that the rejection is obviated by the amendments to claims 1 and 33 to include a chemical structure describing the methionine or methionine-like moiety.

The Office states that the "specification does not enable any person skilled in the art to which it pertains, ... to use the invention commensurate in scope with these claims."[1] However, the authorities establish that a specification that contains a teaching of the manner and process of making and using the invention which corresponds in scope to the claims is presumed to be enabled unless there is reason to doubt the objective truth of the statements contained in the specification.[2] Although the prior art affords no basis for predicting whether a specific sulfur-containing protective agent would be effective against CDDP toxicity, applicant has discovered that ototoxicity due to CDDP can be treated with the limited range of compounds within the structural formula in claim 1. Moreover, with regard to predictability, none of the ineffective sulfur compounds which applicant discusses in the specification on pages 5-9 fall within the structural formula recited in amended claims 1 and 33. And while there still is no basis for predicting the efficacy of many or most species within the wide genus of organic

[1]See Office action dated October 1, 2004 on p. 2.

[2]In re Marzocchi, 169 USPQ 367, 370 (CCPA 1971).

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sulfur compounds, applicants amended claims are diverted to the use of only a relatively small subset of the possible sulfur-containing protective compounds. Accordingly, since applicant is claiming only protective agents of the structural formula in claims 1 and 33, the Office has not provided a reason to doubt the objective truth that these protective agents are enabled for preventing or treating ototoxicity from exposure to anti-tumor platinum-coordination compounds or aminoglycoside antibiotics.

Moreover, inasmuch as there has been no enablement rejection of original claim 2, the provisions of which have now been incorporated into claims 1 and 33, it is believed and understood that the instant amendment fully meets the ground of the enablement rejection of claims 1 and 33 as articulated by the Examiner in the October 1, 2004 Office action. The Office is, therefore, respectfully requested to withdraw the §112, first paragraph rejection of these claims as based on the scope of definition of the sulfur compound.

Because the definition of the protective agent in claim 31 is fully within the scope of the definition of original claim 2, it is further respectfully submitted that the enablement rejection as set forth in the October 1 action does not apply to claim 31. For this reason, and because the claim is independently submitted to be fully enabled under the principles of Marzocchi and similar authorities, it is respectfully submitted that the §112, first paragraph rejection of this claim, as based on the definition of the sulfur compound, should also be withdrawn. Claim 31 is directed to the administration of either L-methionine or D,L-methionine to a patient undergoing treatment with an aminoglycoside antibiotic. No other otoprotective agents are encompassed by this claim. The Examiner has offered no reason to doubt the objective truth of the teaching that L-methionine and D,L-methionine are effective against ototoxicity in a patient undergoing treatment with an aminoglycoside.

Reconsideration is respectfully requested of the rejection of claims 1-45 under 35 U.S.C. § 112 for failure to enable "preventing." The Examiner asserts that generally no compounds in medical science can "prevent" any conditions.[3] However, a medical dictionary defines preventive as "to come before, prevent" and lists prophylactic as a

[3]Page 3 of the Office action dated October 1, 2004.

synonym.[4] Accordingly, the term "prevent" is construed using the plain meaning of the term to mean that the agent is administered prior to the event, as it comes before or is a prophylactic. Additionally, "prevent" does not have the same meaning as the term "cure," because in the medical context, cure implies that the agent is administered after the patient has been in a diseased state, since it is defined as a "restoration to health."[5] Therefore, prevention is not synonymous with cure and a method for preventing ototoxicity as construed above means that the anti-ototoxic agent is administered prior to the event and it does not require a method for treatment with absolute success.

The claims at issue recite methods of "preventing or treating ototoxicity." The definition of "treat" is to care for a patient medically or surgically.[6] When read in the context of the claims and specification as a whole, the meaning of preventing or treating ototoxicity is to administer the otoprotective agent of the invention to a subject in need thereof; this administration could be prior to, simultaneous with or subsequent to the onset of ototoxicity.

Moreover, treating ototoxicity includes preventing ototoxicity. To treat (care for a patient medically) ototoxicity, the care can be prophylactic. In addition, the treatment or care can be simultaneous with or after the onset of the ototoxicity. Thus, to treat ototoxicity, the agents are administered prior to, simultaneous with or after the onset of the ototoxicity; whereas, as detailed above, to prevent ototoxicity, the compositions are administered prior to the onset of the ototoxicity. Neither term requires a "cure."

Reconsideration of the rejection of claims 1-45 under 35 U.S.C. § 112, second paragraph is respectfully requested. As defined in claims 1 and 31, Applicant's invention is directed to a method for

> "preventing or treating ototoxicity in a patient .....undergoing treatment with a chemotherapeutic effective amount of an anti-tumor platinum-coordination compound"

and claim 33 defines Applicants invention in a method for:

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[4]Stedman's Medical Dictionary, 26th Edition, 1995.

[5]See id.

[6]Stedman's Medical Dictionary, 26th Ed., 1995.

preventing or treating ototoxicity in a patient.....undergoing treatment with an aminoglycoside antibiotic."

As the specification states on pages 2-3, anti-tumor platinum-coordination compounds, particularly cisplatin, are known to cause ototoxicity. They inherently possess this potential. Furthermore, the specification states on pages 34-35 that aminoglycoside antibiotics are known to cause ototoxicity. Again, the potential is inherent. Moreover, in many cases, ototoxicity is the dose-limiting factor for administration of anti-tumor platinum-coordination compounds and aminoglycoside antibiotics. Accordingly, with the information in the specification and knowledge in the art, a person of ordinary skill would know that treatment with a chemotherapeutic effective amount of an anti-tumor platinum-coordination compound or an aminoglycoside antibiotic is very likely to cause ototoxicity.

In any event, there is no indefiniteness in the language of claims 1, 31 or 33. With regard to each of these claims, it can readily be determined whether a method as practiced is within the claim or outside of it. Accordingly, there is no necessity for the claim to expressly require that the ototoxicity be "caused by" the platinum-co-ordination compound or by the aminoglycoside. Consistent with practical clinical practice, where either cisplatin or an aminoglycoside is being administered, the method comprises administration of methionine or a defined methionine-like compound as a prophylactic or ameliorative treatment for any ototoxicity that is indicated. The claims in question definitively so provide, and §112, second paragraph is fully satisfied.

Finally, claim 32 was amended to delete the phrase "said noise exposure" as its addition was an inadvertent error.

The Claimed Compounds are Not *prima facie* Obvious in View of the Claims of the Cited Patents.

Reconsideration is requested of the rejection of claims 1-45 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-36 of Campbell (U.S. Patent No. 6,187,817), claims 1-25 of Campbell (U.S. Patent No. 6,265,386) and claims 1-45 [sic 1-29] of copending Application No. 10/694,432.

A. U.S. Patent Nos. 6,187,817 and 6,265,386

Without conceding the propriety of the rejection, applicant's attorney has filed simultaneously herewith a terminal disclaimer with respect to the '817 and '386 patents. Accordingly, the obviousness-type double patenting rejection is traversed with respect to the '817 and '386 patents.

B. U.S. Application Serial No. 10/694,432

The analysis employed in an obvious-type double patenting rejection parallels the guidelines of a 35 U.S.C. § 103 obviousness determination.[7] However, an important distinction exists. A rejection for obviousness must be based on a comparison of the claimed invention to the entirety of the disclosure in the prior art reference, whereas an obviousness-type double patenting rejection must be grounded on a comparison of the claimed invention to the claims, **and only the claims**, of the reference.[8]

The subject matter of the claims of the present application would not have been obvious in view of the claims of copending U.S. Application 10/694,432. When evaluating the scope of a claim, every element of the claim must be considered.[9] To support an obviousness-type double patenting rejection, there must be some motivation or suggestion in the art to modify the claimed process of '432 to incorporate the features of the instantly claimed methods. It is respectfully submitted that the Office has failed to establish any such motivation or suggestion, either by citation of a secondary reference or by evidence of the level of skill in the art or the nature of the problem.

Subject claims 1 and 31 are directed to a method for preventing or treating ototoxicity in a patient undergoing treatment with a chemotherapeutic effective amount of an anti-tumor platinum-coordination compound, the method comprising administering to said patient an effective amount of an otoprotective agent. In contrast, claims 1 and 22 of copending Application 10/694,432 are directed to a method for preventing or

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[7]In re Braat, 937 F.2d 589 (Fed. Cir. 1991).

[8]Purdue Pharma L.P. v. Boehringer Ingelheim GMbH, 98 F.Supp.2d 362, 392, 55 USPQ2d 1168, 1190 (S.D.N.Y. 2000), *aff'd*, 237 F.3d 1359, 57 USPQ2d 1647 (Fed. Cir. 2001).

[9]See, e.g., In re Ochiai, 71 F.3d 1565, 1572, 37 USPQ2d 1127, 1133 (Fed. Cir. 1995).

treating ototoxicity, neurotoxicity, alopecia, gastrointestinal disorder, or reduced survival in a patient exposed to radiation comprising administering to said patient an effective amount of a protective agent. Accordingly, as the claims of the '432 application do not include the element of a "patient undergoing treatment with a chemotherapeutic effective amount of an anti-tumor platinum-coordination compound," the claims do not include all the elements of the subject claims. Furthermore, the claims of the '432 application would not have motivated a person of ordinary skill to select the element of a "patient undergoing treatment with a chemotherapeutic effective amount of an anti-tumor platinum-coordination compound," as radiation is the only cause recited of the toxicities in the '432 claims.

Analogously, subject claim 33 is directed to a method for preventing or treating ototoxicity in a patient undergoing treatment with an aminoglycoside antibiotic. As discussed above, the claims of the '432 application recite radiation as the only cause of the toxicities in the '432 claims, and thus, the '432 claims would not have led a person of ordinary skill to select the element of "treatment with an aminoglycoside antibiotic" from the universe of causes of toxicity. Accordingly, the subject claims would not have been obvious from the claims of the '432 application.

In the Office action it is pointed out that the "comprising" form of the instant claims does not positively exclude the administration of the recited sulfur compounds to a patient who is undergoing treatment with radiation. However, this is not the point. The point is that the instant claims affirmatively require administration to a person who is undergoing treatment with either a platinum-coordination compound or an aminoglycoside antibiotic. Moreover, the '432 claims offer no remote teaching or suggestion that D-methionine or any other sulfur compound be administered to a patient undergoing treatment with a platinum-coordination compound or an aminoglycoside antibiotic. No secondary reference has been cited to support such rejection, nor has the Examiner identified any knowledge within the skill of the art or any motivation in the nature of the problem which would lead from the '432 claims to the instantly claimed method. It is, therefore, respectfully requested that the provisional double patenting rejection over the '432 claims be withdrawn.

Information Disclosure Statement

References 8-75 of the Information Disclosure Statement for the above referenced case and the Information Disclosure Statement in U.S. Application Serial No. 10/694,432 are simultaneously submitted for your review.

Applicant has simultaneously submitted copies of Office actions received in parent applications U.S. Serial No. 09/057,065 (issued as U.S. Pat. No. 6,265,386) and U.S. Ser. No. 08/942,845 (issued as U.S. Pat. No. 6,187,817) along with copies of the pending claim sets corresponding to each Office action.

CONCLUSION

Applicant submits that the present application is now in a condition for allowance and requests early allowance of the pending claims.

Enclosed is a check for $405.00 ($225.00 for a two month extension of time and $180.00 for late submission of an Information Disclosure Statement). The Commissioner is hereby authorized to charge any underpayment and credit any overpayment of government fees to Deposit Account No. 19-1345.

Respectfully submitted,

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JSH/dep

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UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/057,065	04/08/98	CAMPBELL K	SIU7358

000321 HM22/0603
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EXAMINER	
GOLDBERG, J	
ART UNIT	PAPER NUMBER
1614	4

DATE MAILED: 06/03/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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Office Action Summary	Application No. 09/057,065	Applicant(s) Campbell
	Examiner Jerome D. Goldberg	Group Art Unit 1614

☒ Responsive to communication(s) filed on *Mar 8, 1999*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *1* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-29* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☐ Claim(s) _____ is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims *1-29* are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *3*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Claims 1-29 are drawn to an enhanced combination of amino glycoside antibiotic agents, loop diuretic agents, iron chelating agents, quinine or quinidine agent, noise or radiation and a methionine protective agent. Applicant is, therefore, required to elect a single enhanced combination of one specific agent of the above with one specific methionine protective agent and to add a claim to the elected combination. The several inventions above are independent and distinct, each from the other, as they are acquired a separate status in the art as a separate subject matter for inventive effect and require independent searches. It is noted that a reference to one enhanced combination of drugs would not be a reference to another enhanced combination of drugs under 35 U.S.C. 103. Further, the claims read on a multitude of enhanced combinations of drugs which would require many field of searches that would be an undue burden on the Examiner. Therefore, restriction for examination purposes is proper.

Applicant is required to make a provisional election even though this requirement is traversed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner J.D. Goldberg, whose telephone

number is (703) 308-4606. The examiner can normally be reached on Monday through Thursday from 9:00 AM to 3:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Cintins, can be reached on (703) 308-4725. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556 or (703) 305-3592.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

GOLDBERG; aco

May 24, 1999

JEROME D. GOLDBERG
PRIMARY EXAMINER
GROUP 1200

FORM PTO-1449 (REV. 7-80)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DOCKET NO. SIU 7358	SERIAL NO. 09/057,065
	LIST OF PRIOR ART CITED BY APPLICANT (Use several sheets if necessary)	APPLICANT Kathleen C. M. CAMPBELL	
		FILING DATE April 8, 1998	GROUP Not Yet Known

OIPE JUN 11 1998 JC54 PATENT & TRADEMARK OFFICE

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	1	2 7 3 2 4 0 0	01/24/56	Weiss	260	534	
	2	4 4 2 6 3 7 2	01/17/84	Borch	424	10	
	3	5 0 0 2 7 5 5	03/26/91	Mitchell et al.	424	10	
	4	5 2 9 2 7 7 3	03/08/94	Hirsch et al.	514	554	
	5	5 4 3 0 0 6 4	07/04/95	Hirsch et al.	514	554	
	6	5 4 6 6 6 7 8	11/14/95	Kawabata et al.	514	46	

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	7	06 2 0 0 0 4 A1	10/19/94	Europe				

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EXAMINER	DATE CONSIDERED
	5/19/99

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

FORM PTO-1449 (REV. 7-80)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DOCKET NO. SIU 7358	SERIAL NO. 09/057,065
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		FILING DATE April 8, 1998	GROUP Not Yet Known

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			OTHER PRIOR ART (Including Author, Title, Date, Pertinent Pages, Etc.)
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OIPE JC54 JUN 11 1998 PATENT & TRADEMARK OFFICE

			OTHER PRIOR ART (Including Author, Title, Date, Pertinent Pages, Etc.)
	48		Sha et al., "Antioxidant therapy attenuates gentamicin-induced ototoxicity," Abstracts of the Twenty-First Annual Mid-Winter Research Meeting of the Association for Research in Otolaryngology, February 15-19, 1998, Abstract No. 535, p. 134.
	49		Sergio Tognella, "Pharmacological interventions to reduce platinum-induced toxicity," Cancer Treatment Reviews, (1990), 17: 139-142.
	50		Marco Treskes et al., "WR2721 as a modulator of cisplatin- and carboplatin-induced side effects in comparison with other chemoprotective agents: a molecular approach," Cancer Chemotherapy and Pharmacology, (1993), 33: 93-106.
	51		T. Van De Water et al., "Oxidative stress in the inner ear: Combinatorial therapy;" (202) M. B. Rho et al., "Structural evidence for protection from cisplatin ototoxicity by both D- and L-methionine in vivo," Abstracts of the Twenty-First Annual Mid-Winter Research Meeting of the Association for Research in Otolaryngology, February 15-19, 1998, Abstract No. 6, p. 2.
	52		Ernest M. Walker, Jr. et al., "Methods of Reduction of Cisplatin Nephrotoxicity," Annals of Clinical and Laboratory Science, (1981), Vol. 11, No. 5, 397-409.
	53		C. A. Whitworth et al., "Alpha-lipoic acid as a protective agent against ototoxicity;" (535) S. H. Sha et al., "Antioxidant therapy attenuates gentamicin-induced ototoxicity," Abstracts of the Twenty-First Annual Mid-Winter Research Meeting of the Association for Research in Otolaryngology, February 15-19, 1998, Abstract No. 532, p. 134.
	54		Allison Yates Zezulka et al., "Nitrogen Retention in Men Fed Isolated Soybean Protein Supplemented with L-Methionine, D-Methionine, N-Acetyl-L-Methionine, or Inorganic Sulfate," J. Nutr., (1976), 106: 1286-1291.

EXAMINER	DATE CONSIDERED 5/19/99

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

SIU 7358
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Kathleen C.M. Campbell
Serial No.: 09/057,065
Filed: April 8, 1998
For: THERAPEUTIC USE OF D-METHIONINE TO REDUCE THE TOXICITY OF OTOTOXIC DRUGS, NOISE, AND RADIATION

Art Unit: 1614
Examiner: J. D. Goldberg

July 6, 1999
(First business day after July 3, 1999)

RESPONSE TO RESTRICTION AND ELECTION OF SPECIES REQUIREMENT

TO THE COMMISSIONER OF PATENTS AND TRADEMARKS,

SIR:

In response to the Examiner's communication dated June 3, 1999, i.e., Restriction and Election of Species Requirement, Applicant submits the following amendments and remarks in connection with the above-identified application.

Please amend the application as follows:

In the Claims:

Please add the following new claims:

–30. The method of claim 1, wherein said aminoglycoside antibiotic is amikacin, and said methionine protective agent is D-methionine.--

–31. The method of claim 29, wherein said aminoglycoside antibiotic is amikacin.--

What Is Claimed Is:

1. A method for preventing or treating ototoxicity in a patient undergoing treatment with an aminoglycoside antibiotic, comprising administering to said patient an anti-ototoxic effective amount of a methionine protective agent.

2. A method for preventing or treating ototoxicity in a patient undergoing treatment with a loop diuretic agent, comprising administering to said patient an anti-ototoxic effective amount of a methionine protective agent.

3. A method for preventing or treating ototoxicity in a patient undergoing treatment with an iron chelating agent, comprising administering to said patient an anti-ototoxic effective amount of a methionine protective agent.

4. A method for preventing or treating ototoxicity in a patient undergoing treatment with quinine or quinidine, comprising administering to said patient an anti-ototoxic effective amount of a methionine protective agent.

5. A method for preventing or treating ototoxicity in a patient exposed to noise for a time and at an intensity sufficient to result in ototoxicity, comprising administering to said patient an anti-ototoxic effective amount of a methionine protective agent.

6. A method for preventing or treating ototoxicity, neurotoxicity, alopecia, gastrointestinal

disorder, or reduced survival in a patient exposed to radiation for a time and at an intensity sufficient to result in ototoxicity, neurotoxicity, alopecia, gastrointestinal disorder, or reduced survival, comprising administering to said patient an effective amount of a methionine protective agent.

7. The method of claim 1, wherein said methionine protective agent is administered prior to administration of said aminoglycoside antibiotic.

8. The method of claim 1, wherein said methionine protective agent is administered simultaneously with administration of said aminoglycoside antibiotic.

9. The method of claim 1, wherein said methionine protective agent is administered subsequently to administration of said aminoglycoside antibiotic.

10. The method of claim 1, wherein said effective amount of said methionine protective agent is administered to said patient in a time period from about 36 hours before administration of said aminoglycoside antibiotic to about 36 hours after administration of said aminoglycoside antibiotic.

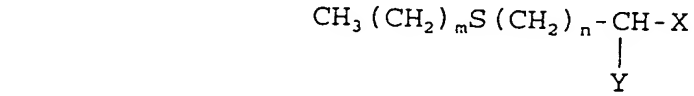
11. The method of claim 1, wherein said effective amount of said methionine protective agent is administered to said patient in a time period from about 25 hours before administration of said aminoglycoside antibiotic to about 25 hours after administration of said aminoglycoside antibiotic.

12. The method of claim 1, wherein said effective amount of said methionine protective agent is administered to said patient in a time period from about 6 hours before administration of said aminoglycoside antibiotic to about 6 hours after administration of said aminoglycoside antibiotic.

13. The method of claim 1, wherein said effective amount of said methionine protective agent is administered to said patient in a time period from about 1 hour before administration of said aminoglycoside antibiotic to about 1 hour after administration of said aminoglycoside antibiotic.

14. The method of claim 1, wherein said effective amount of said methionine protective agent is administered to said patient in a time period from about one-half hour before administration of said aminoglycoside antibiotic to about one-half hour after administration of said aminoglycoside antibiotic.

15. The method of claim 1, wherein said methionine protective agent is a compound having the structural formula:



wherein m is an integer from 0 to 3; n is an integer from 1 to 3; X = $-OR^1$, $-OCOR^1$, $-COOR^1$, $-CHO$, $-CH(OR^1)_2$, or $-CH_2OH$; Y = $-NR^2R^3$ or $-OH$; R^1 = H or a substituted or unsubstituted, straight or branched chain alkyl group having 1 to 6 carbon atoms; R^2 = H or a

substituted or unsubstituted, straight or branched chain acyl group having 1 to 6 carbon atoms; and R^3 = H or a substituted or unsubstituted, straight or branched chain acyl group having 1 to 6 carbon atoms; or

a pharmaceutically acceptable salt thereof.

16. The method of claim 15, wherein said methionine protective agent is in the D-, L-, or DL-form.

17. The method of claim 15, wherein said methionine protective agent is selected from the group consisting of D-methionine, L-methionine, a mixture of D-methionine and L-methionine, methioninol, hydroxy methionine, ethionine, S-adenosyl-L-methionine, a pharmaceutically acceptable salt thereof, and a combination thereof.

18. The method of claim 17, wherein said methionine protective agent is D-methionine.

19. The method of claim 1, wherein said aminoglycoside antibiotic is selected from the group consisting of streptomycin, kanamycin, gentamicin, amikacin, neomycin, netilmicin, paromomycin, vancomycin, hygromycin, erythromycin and tobramycin.

20. The method of claim 1, wherein said effective amount of said methionine protective agent is in the range of from about 0.1 mg/kg body weight to about 500 mg/kg body weight.

21. The method of claim 1, wherein said effective amount of said methionine protective agent is

in the range of from about 1 mg/kg body weight to about 400 mg/kg body weight.

22. The method of claim 1, wherein said effective amount of said methionine protective agent is in the range of from about 10 mg/kg body weight to about 300 mg/kg body weight.

23. The method of claim 1, wherein said effective amount of said methionine protective agent is in the range of from about 1 mg/kg body weight to about 100 mg/kg body weight.

24. The method of claim 1, wherein said effective amount of said methionine protective agent is in the range of from about 10 mg/kg body weight to about 75 mg/kg body weight.

25. The method of claim 1, wherein said methionine protective agent is administered orally or parenterally.

26. The method of claim 25, wherein said parenteral administration is by slow intravenous infusion.

27. The method of claim 1, further comprising administering to said patient a supplemental amount of said methionine protective agent in the range of from about 0.1 mg/kg body weight to about 500 mg/kg body weight per week during and/or after the course of treatment with said aminoglycoside antibiotic.

28. The method of claim 27, wherein said supplemental amount of said methionine protective agent is administered orally or parenterally.

29. A method for preventing or reducing ototoxicity in a patient undergoing treatment with an aminoglycoside antibiotic selected from the group consisting of streptomycin, kanamycin, gentamicin, amikacin, neomycin, netilmicin, paromomycin, vancomycin, hygromycin, erythromycin and tobramycin, comprising:

intravenously administering to said patient

about 10 mg/kg body weight to about 75 mg/kg body weight of D-methionine, or a pharmaceutically acceptable salt thereof,

within about one-half hour before administration of said aminoglycoside antibiotic to about one-half hour after administration of said aminoglycoside antibiotic.

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DEA JKR

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/057,068	04/08/98	CAMPBELL	K 81U7358

000321 HM12/1014
SENNIGER POWERS LEAVITT AND ROEDEL
ONE METROPOLITAN SQUARE
16TH FLOOR
ST LOUIS MO 63102

EXAMINER	
GOLDBERG, I	
ART UNIT	**PAPER NUMBER**
1614	7

DATE MAILED: 10/14/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/057,065	Applicant(s) Campbell
	Examiner Jerome D. Goldberg	Group Art Unit 1614

☒ Responsive to communication(s) filed on *Jul 9, 1999* .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-31* is/are pending in the application.

Of the above, claim(s) *2-6* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1 and 7-31* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *5*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Claims 2-6 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 6.

Applicants elected with traversed in Paper No. 6 the enhanced combination of amikacin and Dimethionine. The restriction required is modified in that the L-, D- or DL methionine are being examined. Applicant's remarks are noted but enhanced combination will support separate patents.

The claims are being examined as they read on the elected combination as modified.

Claims 1 and 7-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the specific aminoglycoside antibiotic and a methionine protective agent, does not reasonably provide enablement for the terms "aminoglycoside antibiotic" and "methionine protective agent." The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The terms "aminoglycoside antibiotic" in claims 1, 7-18 and 20-28 and "methionine protective agent" in claims 1, 7-14, and 19-28 lack clear exemplary support in the specification as filed.

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

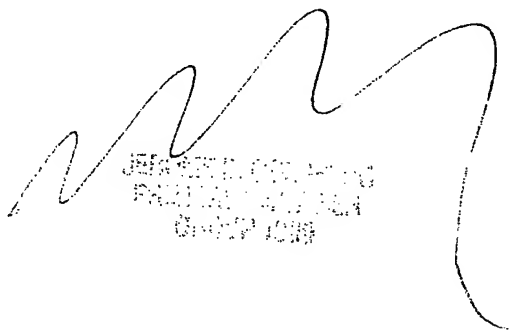
Claims 1 and 7-31 are rejected under 35 U.S.C. 101 because the disclosed invention is inoperative and therefore lacks utility. The Ammash et al reference teaches that the present of

methionine to the medium containing amikacin causes inactivation in the culture. The reference further states that "specific amino acids may interfere with the activity of antibiotics by circumventing their effect on amino acid biosynthesis." Clearly reducing the activity of antibiotic is not seen to be a useful utility. A showing is needed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner J. D. Goldberg whose telephone number is (703) 308-4606. The examiner can normally be reached on Monday through Thursday from 9:00 a.m. to 3:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Cintins, can be reached on (703) 308-4725. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556 or 305-3592.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.



J. Goldberg; CV

10/7/99

Notice of References Cited

Application No.	Applicant(s)		
09/057,065	Campbell		
Examiner		Group Art Unit	Page 1 of 1
Jerome D. Goldberg		1614	

U.S. PATENT DOCUMENTS

	DOCUMENT NO.	DATE	NAME	CLASS	SUBCLASS
A					
B					
C					
D					
E					
F					
G					
H					
I					
J					
K					
L					
M					

FOREIGN PATENT DOCUMENTS

	DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUBCLASS
N						
O						
P						
Q						
R						
S						
T						

NON-PATENT DOCUMENTS

	DOCUMENT (Including Author, Title, Source, and Pertinent Pages)	DATE
U	Ammash et al., Gen. Pharmacol., 25(3), 461-6 ABSTRACT ONLY	1994
V		
W		
X		

SIU 7358
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of Kathleen C. M. Campbell Art Unit 1614
Serial No.: 09/057,065
Filed: April 8, 1998
For: THERAPEUTIC USE OF D-METHIONINE TO REDUCE THE TOXICITY OF OTOTOXIC DRUGS, NOISE, AND RADIATION
Examiner J.D. Goldberg

February 14, 2000

AMENDMENT A

TO THE ASSISTANT COMMISSIONER FOR PATENTS,

SIR:

In response to the Office action of October 14, 1999, the time for response to which is extended to February 4, 2000, under 37 C.F.R. §1.136(a), please enter the following amendments to the above referenced application.

IN THE CLAIMS:

Please add the following new claims:

--32. A method for preventing or treating otoxicity in a patient undergoing treatment with an aminoglycoside antibiotic, comprising administering to said patient an anti-ototoxic effective amount of D-methionine. --

--33. The method of claim 32 wherein said aminoglycoside antibiotic is amikacin.--

REMARKS

Reconsideration of the application claims as amended and in view of the following remarks is respectfully requested.

Amendment

Claims 1 and 7-33 are now in the application and stand ready for action on the merits. Claims 32 and 33 have been added in order to more specifically claim certain embodiments of the present invention. Support for the new claims can be found in the application, for example, as follows:

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UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/057,065	04/09/98	CAMPBELL	K SIU7358

000321 HM22/0614
SENNIGER POWERS LEAVITT AND ROEDEL
ONE METROPOLITAN SQUARE
16TH FLOOR
ST LOUIS MO 63102

EXAMINER	
GOLDBERG, J	
ART UNIT	**PAPER NUMBER**
1614	10

DATE MAILED: 06/13/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (Rev. 2/95)

4/24/00

2 - Mail Copy

Office Action Summary	Application No. 09/057,065	Applicant(s) Campbell
	Examiner Jerome D. Goldberg	Group Art Unit 1614

☒ Responsive to communication(s) filed on *Feb 23, 2000*.

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-33* is/are pending in the application.

Of the above, claim(s) *2-6* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1 and 7-33* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Claims 2-6 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 6.

Cancellation of the non-elected claims is now required.

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1 and 7-33 are rejected under 35 U.S.C. 101 because:

the disclosed invention is inoperative and therefore lacks utility.

The Ammash et al. reference of record teaches that the present of methionine to the medium containing amikacin causes activation in he culture. The reference further states that "specific amino acids may interfere with the activity of antibiotics by circumventing their effect an amino acid biosynthesis". Applicant's remarks and the Dr. Campbell declaration are noted. The declaration shows that the "D-methionine" is effective (see paragraph 16 of the declaration). The claims, however, are directed "comprising" which would employ more than the D-methionine, i.e., DL-methionine.

Claims directed to the D-methionine without the L isomer would overcome this rejection.

Claims 1 and 7-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the specific aminoglycoside antibiotic and methionine protective agent disclosed, does not reasonably provide enablement for the term "aminoglycoside antibiotic" and "methionine protective agent". The specification does not enable any person

skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. .

The terms "aminoglcoside antibiotic" in claims 1, 7-18 and 20-28 and "methionine protective agent" I claims 1, 7-14 and 19-28 lack clear exemplary support. Applicant's remarks are noted but the limited number of examples disclosed will not support such broad terms.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner J. D. Goldberg, whose telephone number is (703) 308-4606. The examiner can normally be reached on Monday-Thursday from 9:00 a.m. to 3:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Cintins, can be reached on (703) 308-4725. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

J. Goldberg:jmr

May 24, 2000

JEROME D GOLDBERG
PRIMARY EXAMINER
GROUP 1200

SIU 7358
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of Kathleen C. M. Campbell Art Unit 1614
Serial No.: 09/057,065
Filed: April 8, 1998
For: THERAPEUTIC USE OF D-METHIONINE TO REDUCE THE TOXICITY OF OTOTOXIC DRUGS, NOISE, AND RADIATION
Examiner J.D. Goldberg

August 11, 2000

AMENDMENT B AFTER FINAL REJECTION

TO THE ASSISTANT COMMISSIONER FOR PATENTS,

SIR:

In response to the Office action of June 14, 2000, please enter the following amendments to the above referenced application.

IN THE CLAIMS:

Please amend claims 1, 7-18, 20-25, 27-28 and 30 as follows:

1. (amended) A method for preventing or treating ototoxicity in a patient undergoing treatment with an aminoglycoside antibiotic, comprising administering to said patient an [anti-ototoxic] effective amount of [a methionine protective] an otoprotective agent comprising D-methionine.

Claim 7, line 2, replace "methionine protective" with --otoprotective--.

Claim 8, line 2, replace "methionine protective" with --otoprotective--.

Claim 9, line 2, replace "methionine protective" with --otoprotective--.

Claim 10, line 2, replace "methionine protective" with --otoprotective--.

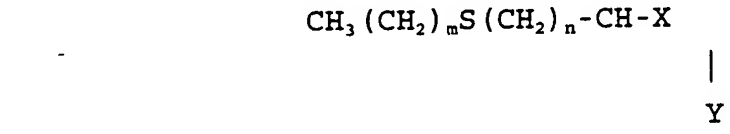
Claim 11, line 2, replace "methionine protective" with --otoprotective--.

Claim 12, line 2, replace "methionine protective" with --otoprotective--.

Claim 13, line 2, replace "methionine protective" with --otoprotective--.

Claim 14, line 2, replace "methionine protective" with --otoprotective--.

15. (amended) The method of claim 1, wherein said [methionine protective] otoprotective agent [is a] further comprises another compound having the structural formula:



wherein m is an integer from 0 to 3; n is an integer from 1 to 3; X = $-OR^1$, $-OCOR^1$, $-COOR^1$, -CHO, $-CH(OR^1)_2$, or $-CH_2OH$; Y = $-NR^2R^3$ or -OH; R^1 = H or a substituted or unsubstituted, straight or branched chain alkyl group having 1 to 6 carbon atoms; R^2 = H or a substituted or unsubstituted, straight or branched chain acyl group having 1 to 6 carbon atoms; and R^3 = H or a substituted or unsubstituted, straight or branched chain acyl group having 1 to 6 carbon atoms; or

a pharmaceutically acceptable salt thereof.

16. (amended) The method of claim [15] 1, wherein said [methionine protective] otoprotective agent [is in the D-, L-, or DL- form] further comprises L-methionine.

Claim 17, line 2, replace "methionine protective" with --otoprotective--.

Claim 18, line 2, replace "methionine protective" with --otoprotective--.

Claim 20, line 2, replace "methionine protective" with --otoprotective--.

Claim 21, line 2, replace "methionine protective" with --otoprotective--.

Claim 22, line 2, replace "methionine protective" with --otoprotective--.

Claim 23, line 2, replace "methionine protective" with --otoprotective--.

Claim 24, line 2, replace "methionine protective" with --otoprotective--.

Claim 25, line 2, replace "methionine protective" with --otoprotective--.

Claim 27, line 3, replace "methionine protective" with --otoprotective--.

Claim 28, line 2, replace "methionine protective" with --otoprotective--.

Claim 30, line 2, replace "methionine protective" with --otoprotective--.

Please add the following new claim:

34. The method of claim 1, wherein said otoprotective agent further comprises D,L-methionine.

REMARKS

Reconsideration of the application claims as amended and in view of the following remarks is respectfully requested.

Amendment

Claims 1 and 7-34 are now in the application and stand ready for action on the merits. Claims 1, 7-18, 20-25, 27-28 and 30 have been amended to replace the term "a methionine protective agent" with "an otoprotective agent comprising D-methionine." Support for the term "otoprotective agent" is found in the specification at page 26, lines 5-7.

New claim 34 has been added. Claim 16 reciting a methionine protective agent in D-, L-, or D,L- form has been further amended as separate claims 16 and 34 directed to the otoprotective agent of claim 1 further comprising L-methionine and D,L-methionine respectively. Support for new claim 34, as well as amended claim 16, can be found in the specification generally at page 29, line 5 through page 32, line 29.

35 U.S.C. §101

Claims 1 and 7-33 stand rejected under 35 U.S.C. §101 because the claimed invention is inoperative and lacks utility over Ammash et al. The Ammash et al. reference is described as teaching that the presence of methionine in a medium containing amikacin causes activation in the culture. However, applicant again respectfully submits that the Examiner's utility rejection is misplaced. As detailed in the February 2000 declaration of Dr. Kathleen C.M. Campbell on record in this case and the remarks

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/057,065	04/08/98	CAMPBELL	K 01U7568

EXAMINER	
GOLDBERG, I	
ART UNIT	**PAPER NUMBER**
1614	12

DATE MAILED: 09/11/00

U00321
SENNIGER POWERS LEAVITT AND ROEDEL
ONE METROPOLITAN SQUARE
16TH FLOOR
ST LOUIS MO 63102

HM12/0911

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (Rev. 2/95)

2 - Mail Copy

Advisory Action

Application No.	Applicant(s)
09/057,065	Campbell
Examiner	**Group Art Unit**
Jerome D. Goldberg	1614

THE PERIOD FOR RESPONSE: [check only a) or b)]

a) ☐ expires _____ months from the mailing date of the final rejection.

b) ☒ expires either three months from the mailing date of the final rejection, or on the mailing date of this Advisory Action, whichever is later. In no event, however, will the statutory period for the response expire later than six months from the date of the final rejection.

Any extension of time must be obtained by filing a petition under 37 CFR 1.136(a), the proposed response and the appropriate fee. The date on which the response, the petition, and the fee have been filed is the date of the response and also the date for the purposes of determining the period of extension and the corresponding amount of the fee. Any extension fee pursuant to 37 CFR 1.17 will be calculated from the date of the originally set shortened statutory period for response or as set forth in b) above.

☐ Appellant's Brief is due two months from the date of the Notice of Appeal filed on _____ (or within any period for response set forth above, whichever is later). See 37 CFR 1.191(d) and 37 CFR 1.192(a).

Applicant's response to the final rejection, filed on *Aug 14, 2000* **has been considered with the following effect, but is NOT deemed to place the application in condition for allowance:**

☒ The proposed amendment(s):

☐ will be entered upon filing of a Notice of Appeal and an Appeal Brief.

☒ will not be entered because:

☐ they raise new issues that would require further consideration and/or search. (See note below).

☐ they raise the issue of new matter. (See note below).

☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal.

☒ they present additional claims without cancelling a corresponding number of finally rejected claims.

NOTE: _____

☐ Applicant's response has overcome the following rejection(s):

_____

☐ Newly proposed or amended claims _____ would be allowable if submitted in a separate, timely filed amendment cancelling the non-allowable claims.

☒ The affidavit, exhibit or request for reconsideration has been considered but does NOT place the application in condition for allowance because:
the Declaration only tested the D isomer, it is not apparent that the other isomers are effective. Claims directed to the D isomer without the L isomer would favorably considered.

☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

☒ For purposes of Appeal, the status of the claims is as follows (see attached written explanation, if any):

Claims allowed: *none*

Claims objected to: *none*

Claims rejected: *1 and 7-33*

☐ The proposed drawing correction filed on _____ ☐has ☐has not been approved by the Examiner.

☐ Note the attached Information Disclosure Statement(s), PTO-1449, Paper No(s). _____ .

☒ Other *Claims 2-6 are with drawn*

JEROME D. GOLDBERG
PRIMARY EXAMINER
ART UNIT 1614

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

RECEIVED FEB 2 1 2001

JED | JAR

NOTICE OF ALLOWANCE AND ISSUE FEE DUE

APPLICATION NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT	DATE MAILED

First Named Applicant	

TITLE OF INVENTION

ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED.

THE ISSUE FEE MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED.

HOW TO RESPOND TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.
If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is changed, pay twice the amount of the FEE DUE shown above and notify the Patent and Trademark Office of the change in status, or
B. If the status is the same, pay the FEE DUE shown above.

If the SMALL ENTITY is shown as NO:

A. Pay FEE DUE shown above, or

B. File verified statement of Small Entity Status before, or with, payment of 1/2 the FEE DUE shown above.

II. Part B-Issue Fee Transmittal should be completed and returned to the Patent and Trademark Office (PTO) with your ISSUE FEE. Even if the ISSUE FEE has already been paid by charge to deposit account, Part B Issue Fee Transmittal should be completed and returned. If you are charging the ISSUE FEE to your deposit account, section "4b" of Part B-Issue Fee Transmittal should be completed and an extra copy of the form should be submitted.

III. All communications regarding this application must give application number and batch number.
Please direct all communications prior to issuance to Box ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

YOUR COPY

Notice of Allowability

Application No.	Applicant(s)
09/057,065	Campbell
Examiner	**Group Art Unit**
Jerome D. Goldberg	1614

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance and Issue Fee Due or other appropriate communication will be mailed in due course.

☒ This communication is responsive to *11/09/2000*.

☒ The allowed claim(s) is/are *1, 7-14, 16, 19-32, and 34*.

☐ The drawings filed on _____ are acceptable.

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

A SHORTENED STATUTORY PERIOD FOR RESPONSE to comply with the requirements noted below is set to EXPIRE **THREE MONTHS** FROM THE "DATE MAILED" of this Office action. Failure to timely comply will result in ABANDONMENT of this application. Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

☐ Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL APPLICATION, PTO-152, which discloses that the oath or declaration is deficient. A SUBSTITUTE OATH OR DECLARATION IS REQUIRED.

☒ Applicant MUST submit NEW FORMAL DRAWINGS

☐ because the originally filed drawings were declared by applicant to be informal.

☐ including changes required by the Notice of Draftsperson's Patent Drawing Review, PTO-948, attached hereto or to Paper No. _____.

☐ including changes required by the proposed drawing correction filed on _____, which has been approved by the examiner.

☐ including changes required by the attached Examiner's Amendment/Comment.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the reverse side of the drawings. The drawings should be filed as a separate paper with a transmittal lettter addressed to the Official Draftsperson.

☐ Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Any response to this letter should include, in the upper right hand corner, the APPLICATION NUMBER (SERIES CODE/SERIAL NUMBER). If applicant has received a Notice of Allowance and Issue Fee Due, the ISSUE BATCH NUMBER and DATE of the NOTICE OF ALLOWANCE should also be included.

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

☒ Interview Summary, PTO-413

☒ Examiner's Amendment/Comment

☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material

☐ Examiner's Statement of Reasons for Allowance

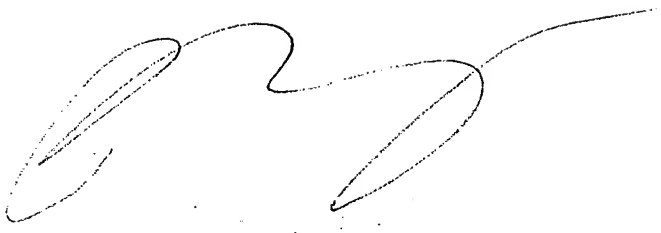
1. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Mr. John K. Roedel, Jr. on November 9, 2000.

2. The application has been amended as follows: Claims 2-6, 15, 17, 18, and 33 have been canceled. The following is an examiner's statement of reasons for allowance: The Dr. Campbell declaration states that methionine "can protect against amikacin-induced hearing loss". This statement clearly shows that the claimed invention is effective.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

3. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jerome D. Goldberg whose telephone number is (703) 308-4606.



JDG

February 13, 2001

Interview Summary

Application No.	Applicant(s)
09/057,065	Campbell
Examiner	**Group Art Unit**
Jerome D. Goldberg	1614

All participants (applicant, applicant's representative, PTO personnel):

(1) *Jerome D. Goldberg* (3) _____

(2) *Mr. John K. Roedel, Jr.* (4) _____

Date of Interview *Nov 9, 2000*

Type: ☒ Telephonic ☐ Personal (copy is given to ☐ applicant ☐ applicant's representative).

Exhibit shown or demonstration conducted: ☐ Yes ☒ No. If yes, brief description:

_____

_____

Agreement ☒ was reached. ☐ was not reached.

Claim(s) discussed: *2-6, 15, 17, 18, and 33*

Identification of prior art discussed:

_____

_____

Description of the general nature of what was agreed to if an agreement was reached, or any other comments:
Ok to cancel claims 2-6, 15, 17, 18, and 33.

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendents which would render the claims allowable is available, a summary thereof must be attached.)

1. ☒ It is not necessary for applicant to provide a separate record of the substance of the interview.

Unless the paragraph above has been checked to indicate to the contrary, A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a response to the last Office action has already been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW.

2. ☒ Since the Examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action. Applicant is not relieved from providing a separate record of the interview unless box 1 above is also checked.

Examiner Note: You must sign and stamp this form unless it is an attachment to a signed Office action.

What Is Claimed Is:

1. A method for preventing or reducing ototoxicity in a patient undergoing treatment with an anti-cancer effective amount of a platinum-containing chemotherapeutic agent, comprising administering to said patient an anti-ototoxic effective amount of a methionine protective agent.

2. A method for preventing or reducing weight loss in a patient undergoing treatment with an anti-cancer effective amount of a platinum-containing chemotherapeutic agent, comprising administering to said patient an anti-weight loss effective amount of a methionine protective agent.

3. A method for preventing or reducing gastrointestinal toxicity in a patient undergoing treatment with an anti-cancer effective amount of a platinum-containing chemotherapeutic agent, comprising administering to said patient an anti-gastrointestinal toxicity effective amount of a methionine protective agent.

4. A method for preventing or reducing neurotoxicity in a patient undergoing treatment with an anti-cancer effective amount of a platinum-containing chemotherapeutic agent, comprising administering to said patient an anti-neurotoxicity effective amount of a methionine protective agent.

5. A method for preventing or reducing alopecia in a patient undergoing treatment with an anti-cancer effective amount of a platinum-containing

chemotherapeutic agent, comprising administering to said patient an anti-alopecia effective amount of a methionine protective agent.

6. A method for prolonging the survival of a patient undergoing treatment with an anti-cancer effective amount of a platinum-containing chemotherapeutic agent, comprising administering to said patient a survival-prolonging effective amount of a methionine protective agent.

7. The method of claim 1, wherein said methionine protective agent is administered prior to administration of said platinum-containing chemotherapeutic agent.

8. The method of claim 1, wherein said methionine protective agent is administered simultaneously with administration of said platinum-containing chemotherapeutic agent.

9. The method of claim 1, wherein said methionine protective agent is administered subsequently to administration of said platinum-containing chemotherapeutic agent.

10. The method of claim 1, wherein said effective amount of said methionine protective agent is administered to said patient in a time period from about 36 hours before administration of said platinum-containing chemotherapeutic agent to about 36 hours after administration of said platinum-containing chemotherapeutic agent.

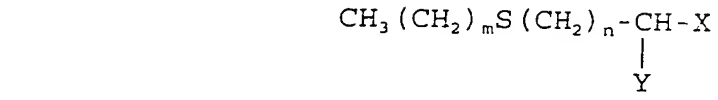
11. The method of claim 1, wherein said effective amount of said methionine protective agent is administered to said patient in a time period from about 25 hours before administration of said platinum-containing chemotherapeutic agent to about 25 hours after administration of said platinum-containing chemotherapeutic agent.

12. The method of claim 1, wherein said effective amount of said methionine protective agent is administered to said patient in a time period from about 6 hours before administration of said platinum-containing chemotherapeutic agent to about 6 hours after administration of said platinum-containing chemotherapeutic agent.

13. The method of claim 1, wherein said effective amount of said methionine protective agent is administered to said patient in a time period from about 1 hour before administration of said platinum-containing chemotherapeutic agent to about 1 hour after administration of said platinum-containing chemotherapeutic agent.

14. The method of claim 1, wherein said effective amount of said methionine protective agent is administered to said patient in a time period from about one-half hour before administration of said platinum-containing chemotherapeutic agent to about one-half hour after administration of said platinum-containing chemotherapeutic agent.

15. The method of claim 1, wherein said methionine protective agent is a compound having the structural formula:



wherein m is an integer from 0 to 3; n is an integer from 1 to 3; X = $-OR^1$, $-OCOR^1$, $-COOR^1$, $-CHO$, $-CH(OR^1)_2$, or $-CH_2OH$; Y = $-NR^2R^3$ or $-OH$; R^1 = H or a substituted or unsubstituted, straight or branched chain alkyl group having 1 to 6 carbon atoms; R^2 = H or a substituted or unsubstituted, straight or branched chain acyl group having 1 to 6 carbon atoms; and R^3 = H or a substituted or unsubstituted, straight or branched chain acyl group having 1 to 6 carbon atoms; or

a pharmaceutically acceptable salt thereof.

16. The method of claim 15, wherein said methionine protective agent is in the D-, L-, or DL-form.

17. The method of claim 15, wherein said methionine protective agent is selected from the group consisting of D-methionine, L-methionine, a mixture of D-methionine and L-methionine, methioninol, hydroxy methionine, ethionine, a pharmaceutically acceptable salt thereof, and a combination thereof.

18. The method of claim 17, wherein said methionine protective agent is D-methionine.

19. The method of claim 1, wherein said platinum-containing chemotherapeutic agent is selected from the group consisting of *cis*-diamminedichloroplatinum(II), *trans*-diaminidichloroplatinum(II), *cis*-diammine-diaquaplatinum(II)-ion, chloro(diethylenetriamine)-platinum(II) chloride, dichloro(ethylenediamine)-platinum(II), diammine(1,1-cyclobutanedicarboxylato)-platinum(II), spiroplatin, dichlorotransdihydroxybisisopropolamine platinum IV (iproplatin), diammine(2-ethylmalonato)-platinum(II), ethylenediaminemalonatoplatinum(II), aqua(1,2-diaminodyclohexane)-sulfatoplatinum(II), (1,2-diaminocyclohexane)malonatoplatinum(II), (4-carboxy-phthalato)(1,2-diaminocyclohexane)-platinum(II), (1,2-diaminocyclohexane)-(isocitrato)platinum(II), (1,2-diaminocyclohexane)-*cis*(pyruvato)platinum(II), and (1,2-diaminocyclohexane)-oxalatoplatinum(II).

20. The method of claim 19, wherein said platinum-containing chemotherapeutic agent is *cis*-diamminedichloro-platinum(II).

21. The method of claim 1, wherein said effective amount of said methionine protective agent is in the range of from about 0.1 mg/kg body weight to about 500 mg/kg body weight.

22. The method of claim 1, wherein said effective amount of said methionine protective agent is in the range of from about 1 mg/kg body weight to about 400 mg/kg body weight.

23. The method of claim 1, wherein said effective amount of said methionine protective agent is

in the range of from about 10 mg/kg body weight to about 300 mg/kg body weight.

24. The method of claim 1, wherein said effective amount of said methionine protective agent is in the range of from about 1 mg/kg body weight to about 100 mg/kg body weight.

25. The method of claim 1, wherein said effective amount of said methionine protective agent is in the range of from about 10 mg/kg body weight to about 75 mg/kg body weight.

26. The method of claim 1, wherein said effective amount of said methionine protective agent in relation to said anti-cancer effective amount of said platinum-containing chemotherapeutic agent is in the range of from about 4:1 to about 167:1, methionine protective agent:platinum-containing chemotherapeutic agent, on a molar basis.

27. The method of claim 1, wherein said effective amount of said methionine protective agent in relation to said anti-cancer effective amount of said platinum-containing chemotherapeutic agent is in the range of from about 4.25:1 to about 100:1, methionine protective agent:platinum-containing chemotherapeutic agent, on a molar basis.

28. The method of claim 1, wherein said effective amount of said methionine protective agent in relation to said anti-cancer effective amount of said platinum-containing chemotherapeutic agent is in the range of from about 4.68:1 to about 20:1, methionine

protective agent:platinum-containing chemotherapeutic agent, on a molar basis.

29. The method of claim 1, wherein said effective amount of said methionine protective agent in relation to said anti-cancer effective amount of said platinum-containing chemotherapeutic agent is about 18.75:1, methionine protective agent:platinum-containing chemotherapeutic agent, on a molar basis.

30. The method of claim 1, wherein said methionine protective agent is administered orally or parenterally.

31. The method of claim 30, wherein said platinum-containing chemotherapeutic agent is administered parenterally.

32. The method of claim 31, wherein said parenteral administration is by slow intravenous infusion.

33. The method of claim 1, further comprising administering to said patient a supplemental amount of said methionine protective agent in the range of from about 0.1 mg/kg body weight to about 500 mg/kg body weight per week during and/or after the course of treatment with said platinum-containing chemotherapeutic agent.

34. The method of claim 33, wherein said supplemental amount of said methionine protective agent is administered orally or parenterally.

35. A method for preventing or reducing ototoxicity in a patient undergoing treatment with an anti-cancer effective amount of a platinum-containing chemotherapeutic agent selected from the group consisting of cisplatin, carboplatin, and iproplatin, comprising:

intravenously administering to said patient

about 10 mg/kg body weight to about 75 mg/kg body weight of D-methionine, or a pharmaceutically acceptable salt thereof, or

D-methionine or a pharmaceutically acceptable salt thereof in a molar ratio of about 18.75:1, D-methionine:platinum-containing chemotherapeutic agent,

within about one-half hour before administration of said platinum-containing chemotherapeutic agent to about one-half hour after administration of said platinum-containing chemotherapeutic agent.

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

RECD JUN 0 2 1998

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/942,140	10/02/97	CAMPBELL K	61U7356

CEC/JKR

000321 HN42/0529
SENNIGER, POWERS, LEAVITT, & ROEDEL
ONE METROPOLITAN SQUARE
16TH FLOOR
ST LOUIS MO 63102

EXAMINER	
GOLDBERG, J	

ART UNIT	PAPER NUMBER
1514	

DATE MAILED: 05/29/98

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/942,845	Applicant(s) Campbell
	Examiner Jerome D. Goldberg	Group Art Unit 1614

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *1* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-35* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☐ Claim(s) _____ is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims *1-35* are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- *SEE OFFICE ACTION ON THE FOLLOWING PAGES* ---

Claims 1-35 are drawn to the enhanced combination of a platinum - containing chemotherapeutic agent and a methionine protective agent. Applicant is required to elect a single enhanced combination of one platinum containing chemotherapeutic agent with one methionine protective agent and to add a claim to the specific enhanced combination.

The several inventions above are independent and distinct, each from the other, as they have acquired a separate status in the art as a separate subject matter for inventive effect and require independent searches. It is noted that a reference to one enhanced combination of drugs would not be a reference to another enhanced combination of drugs under 35 U.S.C. 103. Further, the claims read on a multitude of enhanced combinations of drugs which would require many field of searches that would be an undue burden on the Examiner. Therefore, restriction for examination purpose is proper.

Applicant is required to make a provisional election even though this requirement is traversed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner J.D. Goldberg whose telephone

number is (703) 308-4606. The examiner can normally be reached on Monday through Thursday from 9:00 AM to 3:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Cintins, can be reached on (703) 308-4725. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556 or (703) 305-3592.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

GOLDBERG; aco

May 22, 1998

JEROME D. GOLDBERG
PRIMARY EXAMINER
GROUP 1200

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Kathleen C.M. Campbell Art Unit: 1614
Serial No.: 08/942,845 Examiner: J. Goldberg
Filed: October 2, 1997
For: THERAPEUTIC USE OF D-METHIONINE TO REDUCE THE TOXICITY OF PLATINUM-CONTAINING ANTI-TUMOR COMPOUNDS

June 5, 1998

RESPONSE TO ELECTION OF SPECIES REQUIREMENT

AND AMENDMENT "A"

TO THE ASSISTANT COMMISSIONER FOR PATENTS,

SIR:

In response to the Examiner's communication dated May 29, 1998, i.e., Election of Species Requirement, Applicant submits the following amendments and remarks in connection with the above-identified application.

Please amend the application as follows:

In the Claims:

Please add the following new claims:

-- 36. The method of claim 1, wherein said platinum-containing chemotherapeutic agent is cisplatin, and said methionine protective agent is D-methionine.--

-- 37. The method of claim 2, wherein said platinum-containing chemotherapeutic agent is cisplatin, and said methionine protective agent is D-methionine.--

-- 38. The method of claim 3, wherein said platinum-containing chemotherapeutic agent is cisplatin, and said methionine protective agent is D-methionine.--

-- 39. The method of claim 4, wherein said platinum-containing chemotherapeutic agent is cisplatin, and said methionine protective agent is D-methionine.--

-- 40. The method of claim 5, wherein said platinum-containing chemotherapeutic agent is cisplatin, and said methionine protective agent is D-methionine.--

-- 41. The method of claim 6, wherein said platinum-containing chemotherapeutic agent is cisplatin, and said methionine protective agent is D-methionine.--

R E M A R K S

Claims 36-41 have been newly added in response to the Examiner's requirement that a claim drawn to an enhanced combination of a platinum-containing anti-tumor compound with a methionine protective agent be added. Thus, claims 1-41 are now in the application, and stand ready for action on the merits.

The Examiner has required Applicant to elect a single disclosed enhanced combination of a platinum-containing anti-tumor compound with a methionine protective agent, and to add a claim thereto, in order to commence examination of the present application. This requirement is respectfully traversed. Reconsideration and withdrawal thereof are requested.

Applicant submits that there is a close nexus among the various platinum-containing anti-tumor compound species, as well as among the methionine protective agent species, of the present application, and substantially overlapping searches for combinations thereof.

Therefore, for the foregoing reasons, the Examiner is respectfully requested to reconsider the present Election of Species Requirement set forth in the outstanding Office Action, withdraw the same, and proceed to examine all the claims of the present application together on their merits.

However, so as to be fully responsive to the Election of Species Requirement, Applicant hereby elects, with traverse, the combination of cisplatin and D-methionine for further prosecution in the present application.

RECD JUL 0 6 1998

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/942,645	10/02/97	CAMPBELL	K STU7356

CEC KER

000321 HM42/0701
SCHNIGER, POWERS, LEAVITT, & ROEDEL
ONE METROPOLITAN SQUARE
16TH FLOOR
ST LOUIS MO 63102

EXAMINER	
GOLDBERG, J	
ART UNIT	**PAPER NUMBER**
1614	

DATE MAILED: 07/01/98

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

7/7/98
7/7/98

CEC
CEC

☆U.S.GOVERNMENT PRINTING OFFICE 1996-411-516/40275

Office Action Summary	Application No. 08/942,845	Applicant(s) Campbell
	Examiner Jerome D. Goldberg	Group Art Unit 1614

☒ Responsive to communication(s) filed on *Jun 8, 1998*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-41* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-41* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Applicant elected the specific enhanced combination of cisplatin and D-methionine with traversed in Paper No. 5. The restriction requirement is herein modified in that the D and DL methionine will be examined with the cisplatin.

The claims are being examined as they read on the elected enhanced combination of cisplatin and methionine.

The Bibliography on pages 39-51 should be deleted and presented on a PTO form 1449 along with the references.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over the Newman et al reference.

The Newman et al reference teaches cisplatin at 16 mg/kg with methionine being administered 15 minutes before or one hour after the cisplatin with "decrease.. The toxicity of the Pt compd." (last two lines). In view of this, one skilled would be motivated to employ methionine to reduced the toxify of cisplatin. Clearly the specific toxic ~~if both~~ effects being claimed would be reduced by employing methionine.

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-41 are rejected under 35 U.S.C. 101 because the disclosed invention is inoperative and therefore lacks utility. The Alden et al reference teaches that methionine enhances the nephrotoxicity of cisplatin.

Clearly a comparison with applicant's method vs the Alden et al reference is needed.

Claims 1-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the specific platinum-containing chemotherapeutic agent and a methionine protective agent disclosed, does not reasonably provide enablement for the terms "platinum - containing chemotherapeutic agent" in claims 1-18 and 21-35 and" a methionine protective agent: in claims 1-14 and 19-35 lacks clear exemplary support in the specification as filed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner J. D. Goldberg whose telephone number is (703) 308-4606. The examiner can normally be reached on Monday-Thursday from 9:00 a.m. to 3:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Cintinis, can be reached on (703) 308-4725. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

J. Goldberg:jmr

June 25, 1998

JEROME D. GOLDBERG
PRIMARY EXAMINER
GROUP 1200

Notice of References Cited

Application No.	Applicant(s)		
08/942,845	Campbell		
Examiner		Group Art Unit	Page 1 of 1
Jerome D. Goldberg		1614	

U.S. PATENT DOCUMENTS

	DOCUMENT NO.	DATE	NAME	CLASS	SUBCLASS
A					
B					
C					
D					
E					
F					
G					
H					
I					
J					
K					
L					
M					

FOREIGN PATENT DOCUMENTS

	DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUBCLASS
N						
O						
P						
Q						
R						
S						
T						

NON-PATENT DOCUMENTS

	DOCUMENT (Including Author, Title, Source, and Pertinent Pages)	DATE
U	Newman et al.,J. Clem. Hematol. Oncol., 9 (2), 208-9 ABSTRACT ONLY	1979
V	Alden et al., Chem. -Biol. Interact., 48(1), 121-4 ABSTRACT ONLY	1984
W		
X		

AN 1979:449506 CAPLUS
DN 91:49506
TI Inhibition of biological activity of **cisplatin** by thiourea and L-**methionine**
AU Newman, Andrew D.; Ridgway, Helen; Speer, Robert J.; Hill, Joseph M.
CS Dep. Chem., Wadley Inst. Mol. Med., Dallas, TX, USA
SO J. Clin. Hematol. Oncol. (1979), 9(2), 208-9
CODEN: JCHODP
DT Journal
LA English
CC 1-5 (Pharmacodynamics)
AB In expts. using mice with leukemia L1210, the survival following treatment with 8 mg/kg **cisplatin** [15663-27-1] was decreased when thiourea [62-56-6] or L-**methionine** [63-68-3] was administered 15 min before or 1 h after the Pt drug, owing to a decrease in the antitumor effectiveness of the Pt drug. However, when 16 mg/kg **cisplatin** was used, thiourea and L-**methionine** increased survival, owing to a decrease in the toxicity of the Pt compd.
ST **cisplatin** antitumor toxicity **methionine** thiourea
IT 62-56-6, biological studies 63-68-3, biological studies
RL: BIOL (Biological study)
(**cisplatin** antitumor activity and toxicity response to)
IT 15663-27-1
RL: BIOL (Biological study)
(neoplasm inhibition by toxicity of, **methionine** and thiourea effect on)

AN 1984:167801 CAPLUS
DN 100:167801
TI Exacerbation of **cisplatin**-induced nephrotoxicity by **methionine**
AU Alden, W. Wesley; Repta, A. J.
CS Dep. Pharm. Chem., Univ. Kansas, Lawrence, KS, 66045, USA
SO Chem.-Biol. Interact. (1984), 48(1), 121-4
CODEN: CBINA8; ISSN: 0009-2797
DT Journal
LA English
CC 1-6 (Pharmacology)
AB In rats, bolus i.v. injection of **cisplatin** [15663-27-1] and subsequent administration of **methionine** [63-68-3] increased the nephrotoxicity of **cisplatin** as judged by an increase in blood urea N (BUN). Thus, **methionine**, which may form complexes with **cisplatin** in vivo, enhances the nephrotoxicity of the antitumor drug.
ST **cisplatin** nephrotoxicity **methionine**
IT Kidney, toxic chemical and physical damage
(**cisplatin** toxicity to, **methionine** exacerbation of)
IT 63-68-3, biological studies
RL: BIOL (Biological study)
(**cisplatin** toxicity to kidney exacerbation by)
IT 15663-27-1
RL: PRP (Properties)
(toxicity of, to kidney, **methionine** exacerbation of)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Kathleen C.M. Campbell

Examiner: J.D. Goldberg

Serial No.: 08/942,845

Art Unit: 1614

Filed: October 2, 1997

For: THERAPEUTIC USE OF D-METHIONINE TO REDUCE THE TOXICITY OF PLATINUM-CONTAINING ANTI-TUMOR COMPOUNDS

October 1, 1998

AMENDMENT B

RESPONSE UNDER 37 C.F.R. 1.111

TO THE ASSISTANT COMMISSIONER FOR PATENTS,

SIR:

In response to the Examiner's Office Action dated July 1, 1998, Applicant submits the following amendments and remarks in connection with the above-identified application.

In the Claims:

Please amend the claims as follows:

1.(Amended) A method for preventing or reducing ototoxicity in a patient selected from the group consisting of a human, a cat, and a dog undergoing treatment with an anti-cancer effective amount of a platinum-containing chemotherapeutic agent, comprising administering to said patient an anti-ototoxic effective amount of a methionine protective agent.

2.(Amended) A method for preventing or reducing weight loss in a patient selected from the group consisting of a human, a cat, and a dog undergoing treatment with an anti-

cancer effective amount of a platinum-containing chemotherapeutic agent, comprising administering to said patient an anti-weight loss effective amount of a methionine protective agent.

3.(Amended) A method for preventing or reducing gastrointestinal toxicity in a patient selected from the group consisting of a human, a cat, and a dog undergoing treatment with an anti-cancer effective amount of a platinum-containing chemotherapeutic agent, comprising administering to said patient an anti-gastrointestinal toxicity effective amount of a methionine protective agent.

4.(Amended) A method for preventing or reducing neurotoxicity in a patient selected from the group consisting of a human, a cat, and a dog undergoing treatment with an anti-cancer effective amount of a platinum-containing chemotherapeutic agent, comprising administering to said patient an anti-neurotoxicity effective amount of a methionine protective agent.

5.(Amended) A method for preventing or reducing alopecia in a patient selected from the group consisting of a human, a cat, and a dog undergoing treatment with an anti-cancer effective amount of a platinum-containing chemotherapeutic agent, comprising administering to said patient an anti-alopecia effective amount of a methionine protective agent.

6.(Amended) A method for prolonging the survival of a patient selected from the group consisting of a human, a cat, and a dog undergoing treatment with an anti-cancer effective amount of a platinum-containing chemotherapeutic agent, comprising administering to said patient a survival-prolonging effective amount of a methionine protective agent.

REMARKS

Claims 1-6 have been amended to clarify the invention. Support for these amendments can be found in the specification as originally filed at, for example, page 1, lines 9-11, and page 27, lines 8 and 14-16. Entry thereof is therefore believed to be in order, and is respectfully requested. Claims 1-41 are in the application, and stand ready for action on the merits. Reexamination and reconsideration of the present application in view of the amendments and remarks presented herein are respectfully requested.

RECEIVED JAN 11 1999

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/942,845	10/02/97	CAMPBELL	813/350

CEC JKR

000321
SENNIGER POWERS LEAVITT AND ROEDEL
ONE METROPOLITAN SQUARE
16TH FLOOR
ST LOUIS MO 63102

HM42/0106

EXAMINER	
GUILDOEANS, J	

ART UNIT	PAPER NUMBER
1614	10

DATE MAILED: 01/06/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/942,845	Applicant(s) Campbell
	Examiner Jerome D. Goldberg	Group Art Unit 1614

☒ Responsive to communication(s) filed on *Oct. 5, Oct. 9, and Nov. 13, 1998* .

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-41* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-41* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *9*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Applicant elected the specific enhanced combination of cisplatin and methionine with traversed in Paper No. 5. The claims are still being examined as they read on the elected enhanced combination of cisplatin and methionine. Cancellation of non-elected subject matter from the claims is now required.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over the Newman et al. reference of record including the copy, present by applicant (Paper No. 8) for the reasons fully set forth in Paper No. 6, page 2.

Applicant's remarks are noted but the Newman et al. reference on page 209, lines 7-9 states that "with the higher cisplatin dose, thiourea and L-methionine reduced the toxicity". With regard to using 8mg/kg, clearly there is no benefit but the application of 16mg/kg there is an active effect. It is noted that the same drugs are being administered together the results should be same.

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-41 are rejected under 35 U.S.C. 101 because the Alden et al. reference (newly presented by applicant) clearly teaches an opposite effect. The reference page 123, lines 30-32 state that "consequently, it may be clinically useful to attempt to reduce the endogenous methionine levels prior to treatment with cisplatin". Applicant's remarks are noted but a showing is needed.

Claims 1-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the specific platinum-containing chemotherapeutic agent and methionine protective agent disclosed, does not reasonably provide enablement for the terms "platinum-containing chemotherapeutic agent" and "methionine protective agent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The terms "platinum-containing chemotherapeutic agent" in claims 1-18 and 21-35 and "methionine protective agent" in claims 1-14 and 19-35 lack clear in the

specification. Applicant's remarks are noted but the limited number of examples set forth will not support such broad terms. Moreover, it not apparent that all combination are in fact effective. (Note the above rejection).

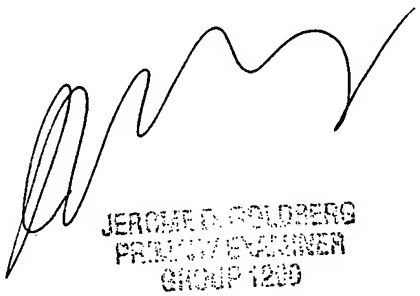
Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner J.D. Goldberg, whose telephone number is (703) 308-4606. The examiner can normally be reached on Monday through Thursday from 9:00 AM to 3:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Cintins, can be reached on (703) 308-4725. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.



GOLDBERG; aco

December 31, 1998

Sheet 1 of 1

FORM PTO-1449 (REV. 7-80)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DOCKET NO. SIU 7356	SERIAL NO. 08/942,845
LIST OF PRIOR ART CITED BY APPLICANT (Use several sheets if necessary)		APPLICANT Kathleen C. M. Campbell	
		FILING DATE October 2, 1997	GROUP 1614

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U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO

OTHER PRIOR ART (Including Author, Title, Date, Pertinent Pages, Etc.)

	55		Burchenal, J. H., et al., "Studies of cross-resistance, synergistic combinations and blocking of activity of platinum derivatives," *Biochimie*, 60:961-965, 1978.
	56		Drewinko, B., et al., "The Effect of *cis*-Diamminedichloroplatinum(II) on Cultured Human Lymphoma Cells and Its Therapeutic Implications," *Cancer Research*, 33:3091-3095, December 1973.
	57		Drobnik, Jaroslav, et al., "Inactivation Of Bacteriophages With *Cis*-Platinum(II) Diamminedichloride," *Chem.-Biol. Interactions*, 11:365-375, 1975.
	58		Friedman, M. E., et al., "The Blocking Of The Tetrachloroplatinate(II) Inhibition Of Malate Dehydrogenase By Sulfur-Containing Amino Acids," *Biochimica et Biophysica Acta*, 341:277-283, 1974.
	59		Hayes, D., et al., "Amelioration Of Renal Toxicity Of High Dose Cis-Platinum Diammine Dichloride (CPDD) By Mannitol Induced Diuresis," *Proc. Am. Assoc. Cancer Res.*, 17:169, 1976. ABSTRACT ONLY
	60		Merrin, Claude, "A New Method To Prevent Toxicity With High Doses Of Cis Diammine Platinum (Therapeutic Efficacy In Previously Treated Widespread And Recurrent Testicular Tumors)," *Proc. Am. Assoc. Cancer Res.*, 17:243, 1976. ABSTRACT ONLY
	61		Speer, R. J., et al., "Coordination Complexes of Platinum as Antitumor Agents," *Cancer Chemotherapy Reports*, Part I, Vol. 59, No. 3, pp. 629-641, 1975.
	62		Ward, J. M., et al., "Modification of the Renal Toxicity of *cis*-Dichlorodiammineplatinum(II) With Furosemide in Male F344 Rats," *Cancer Treatment Reports*, Vol. 61, No. 3, pp. 375-379, 1977.

EXAMINER	DATE CONSIDERED 1-29-99

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Sheet 1 of 1

FORM PTO-1449 (REV. 7-80)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DOCKET NO. SIU 7356	SERIAL NO. 08/942,845
LIST OF PRIOR ART CITED BY APPLICANT (Use several sheets if necessary)		APPLICANT Kathleen C. M. Campbell	
		FILING DATE October 2, 1997	GROUP 1614

O I P E NOV 1 3 1998 PATENT & TRADEMARK OFFICE

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE

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FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO

OTHER PRIOR ART (Including Author, Title, Date, Pertinent Pages, Etc.)

[initials]	55		Burchenal, J. H., et al., "Studies of cross-resistance, synergistic combinations and blocking of activity of platinum derivatives," *Biochimie*, 60:961-965, 1978.
[initials]	56		Drewinko, B., et al., "The Effect of *cis*-Diamminedichloroplatinum(II) on Cultured Human Lymphoma Cells and Its Therapeutic Implications," *Cancer Research*, 33:3091-3095, December 1973.
[initials]	57		Drobnik, Jaroslav, et al., "Inactivation Of Bacteriophages With *Cis*-Platinum(II) Diamminedichloride," *Chem.-Biol. Interactions*, 11:365-375, 1975.
[initials]	58		Friedman, M. E., et al., "The Blocking Of The Tetrachloroplatinate(II) Inhibition Of Malate Dehydrogenase By Sulfur-Containing Amino Acids," *Biochimica et Biophysica Acta*, 341:277-283, 1974.
[initials]	59		Hayes, D., et al., "Amelioration Of Renal Toxicity Of High Dose Cis-Platinum Diammine Dichloride (CPDD) By Mannitol Induced Diuresis," *Proc. Am. Assoc. Cancer Res.*, 17:169, 1976. ABSTRACT ONLY
[initials]	60		Merrin, Claude, "A New Method To Prevent Toxicity With High Doses Of Cis Diammine Platinum (Therapeutic Efficacy In Previously Treated Widespread And Recurrent Testicular Tumors)," *Proc. Am. Assoc. Cancer Res.*, 17:243, 1976. ABSTRACT ONLY
[initials]	61		Speer, R. J., et al., "Coordination Complexes of Platinum as Antitumor Agents," *Cancer Chemotherapy Reports*, Part I, Vol. 59, No. 3, pp. 629-641, 1975.
[initials]	62		Ward, J. M., et al., "Modification of the Renal Toxicity of *cis*-Dichlorodiammineplatinum(II) With Furosemide in Male F344 Rats," *Cancer Treatment Reports*, Vol. 61, No. 3, pp. 375-379, 1977.

EXAMINER [signature]	DATE CONSIDERED 12/29/98

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Kathleen C.M. Campbell
Serial No.: 08/942,845
Filed: October 2, 1997
For: Therapeutic Use of D-Methionine to Reduce the Toxicity of Platinum-Containing Antitumor Compounds

Art Unit: 1614
Examiner: J. Goldberg

March 8, 1999
(First business day after March 6, 1999)

Amendment C

RESPONSE UNDER 37 C.F.R.1.116

TO THE ASSISTANT COMMISSIONER FOR PATENTS,
Washington, D.C. 20231

SIR:

In response to the Examiner's final Office Action dated January 6, 1999, Applicant submits the following proposed amendments and remarks in connection with the above-identified application.

In the Claims:

Please cancel claims 6 and 41 without prejudice or disclaimer of any of the subject matter contained therein.

REMARKS

Claims 6 and 41 have been cancelled. Thus, claims 1-5 and 7-40 are in the application, and stand ready for action on the merits. Reexamination and reconsideration of the present application in view of the following proposed remarks are respectfully requested.

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UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APR 15 19

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/942,345	10/02/97	CAMPBELL K	SIU7358

000321 CEC JKR HM12/0409
SENNIGER POWERS LEAVITT AND ROEDEL
ONE METROPOLITAN SQUARE
16TH FLOOR
ST LOUIS MO 63102

EXAMINER
GOLDBERG, J

ART UNIT	PAPER NUMBER
1614	13

DATE MAILED: 04/09/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Not appealed date 7-6-99 or pursuant to docketed

PTO-90C (Rev. 2/95)
*U.S. GPO: 1997-417-381/62715

2 - Mail Copy

Advisory Action

Application No.	Applicant(s)
08/942,845	Campbell
Examiner	**Group Art Unit**
Jerome D. Goldberg	1614

THE PERIOD FOR RESPONSE: [check only a) or b)]

a) ☐ expires _____ months from the mailing date of the final rejection.

b) ☒ expires either three months from the mailing date of the final rejection, or on the mailing date of this Advisory Action, whichever is later. In no event, however, will the statutory period for the response expire later than six months from the date of the final rejection.

Any extension of time must be obtained by filing a petition under 37 CFR 1.136(a), the proposed response and the appropriate fee. The date on which the response, the petition, and the fee have been filed is the date of the response and also the date for the purposes of determining the period of extension and the corresponding amount of the fee. Any extension fee pursuant to 37 CFR 1.17 will be calculated from the date of the originally set shortened statutory period for response or as set forth in b) above.

☐ Appellant's Brief is due two months from the date of the Notice of Appeal filed on _____ (or within any period for response set forth above, whichever is later). See 37 CFR 1.191(d) and 37 CFR 1.192(a).

Applicant's response to the final rejection, filed on *Mar 12, 1999* **has been considered with the following effect, but is NOT deemed to place the application in condition for allowance:**

☒ The proposed amendment(s):

☒ will be entered upon filing of a Notice of Appeal and an Appeal Brief.

☐ will not be entered because:

☐ they raise new issues that would require further consideration and/or search. (See note below).

☐ they raise the issue of new matter. (See note below).

☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal.

☐ they present additional claims without cancelling a corresponding number of finally rejected claims.

NOTE: _____

☒ Applicant's response has overcome the following rejection(s):
Claims 1-41 under 35 USC 101

☐ Newly proposed or amended claims _____ would be allowable if submitted in a separate, timely filed amendment cancelling the non-allowable claims.

☒ The affidavit, exhibit or request for reconsideration has been considered but does NOT place the application in condition for allowance because:
a showing over the prior art reference is needed.

☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

☒ For purposes of Appeal, the status of the claims is as follows (see attached written explanation, if any):

Claims allowed: *none*

Claims objected to: *none*

Claims rejected: *1-5 and 7-40*

☐ The proposed drawing correction filed on _____ ☐has ☐has not been approved by the Examiner.

☒ Note the attached Information Disclosure Statement(s), PTO-1449, Paper No(s). *11*

☐ Other

JEROME D. GOLDBERG
PRIMARY EXAMINER
GROUP 1610

FORM PTO-1449 (REV. 7-80)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DOCKET NO. SIU 7356	SERIAL NO. 08/942,845
	LIST OF PRIOR ART CITED BY APPLICANT (Use several sheets if necessary)	APPLICANT Kathleen C. M. Campbell	
		FILING DATE October 2, 1997	GROUP 1614

O I P E JCB FEB 22 1999 PATENT & TRADEMARK OFFICE

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE

OTHER PRIOR ART (Including Author, Title, Date, Pertinent Pages, Etc.)

	63		Cardini, G., et al., "La Radioprotezione Dei Cromosomi Delle Cellule Midollari Umane In Vitro," *Radiobiologia Radioterapia E Fisica Medica*, Vol. 22, No. 6, pp. 371-375, 1967. SUMMARY ONLY
	64		Carrithers, S. L., et al., "Methylation Of Radiation Protector Compounds By Thiol Methyltransferase," *FASEB*, Vol. 5, No. 4, pg. A824, 1991. ABSTRACT ONLY
	65		Correa, J. N., et al., "Radiosensitization and radioprotection on murine chondrosarcoma," *Radiation Research*, Vol. 74, No. 3, pg. 517, 1978. ABSTRACT ONLY
	66		~~De Vecchi, A., "Sperimentazione Clinica Di Una Nuova Sostanza Radioprotettiva (Cloruro Di Metil-Metionin-Sulfonio)," *Radiobiologia Radioterapia E Fisica Medica*,, Vol. 22, No. 5, pp. 355-370, 1967.~~ SUMMARY ONLY
	67		Gessler, N., et al., "Antiradiation effects of S-methylmethionine (Vitamin U)," *Prikl. Biokhim. Mikrobiol.*, Vol. 32, No. 6, pp. 666-668, 1996. ABSTRACT ONLY
	68		Infante, G. A., et al., "Chemical radioprotection on biological important compounds," *Radiation Research*, Vol. 67, No. 3, pg. 637, 1976. ABSTRACT ONLY
	69		~~Kido, K., "The influence of methylmethionine sulfonium-chloride (MMSC) on survivors of mice after X-ray irradiation, especially the consideration of the drug effect for the degeneration of intestinal mucosa," *Kansai-Ika Daigaku Zasshi*, Vol. 25, No. 1, pp. 104-107, 1973.~~ Translation needed
	70		Kovács, V., et al., "Study of the Radiation Protection Effect of Selenium-Methionine by Determining the Paramagnetic Properties of Liver Tissues of Mice," *Acta Physica Hungarica*, Vol. 64, No. 1-3, pp. 321-326, 1988.
	71		Mekhtiev, M. A., et al., "Radioprotective effect during the separate and combined use of DL-methionine and thyroxine," *Database Chemabs Chemical Abstracts Service*, Abstract No. 76:54431, 1970 (see also *Tr. Inst. Fiziol., Akad. Nauk Azerb. SSR*, Vol. 11, pp. 83-100, 1970). ABSTRACT ONLY
	72		Molteni, F., et al., "The use of S-adenosyl-methionine as a radioprotective agent," *Gazetta Medica Italiana*, Vol. 137, No. 7-8, pp. 303-308, 1978. SUMMARY ONLY
	73		Salikhodzhaev, Z., et al., "Stimulation of postirradiation recovery of rat haemopoiesis by a cobalt preparation," *Database Biosis Biosciences Information Service*, Philadelphia, Pennsylvania, Abstract No. 08095385 (see also *Radiobiologya*, Vol. 31, No. 6, pp. 835-837, 1991). ABSTRACT ONLY
	74		Romito, S., "Sulla radioprotezione cromosomica in vitro: esperienze con metionina, acido aspartico, leucina, lisina," *Fracastoro*, Vol. 62, No. 6, pp. 576-581, 1969. SUMMARY ONLY
	75		Srinivasan, V., et al., "Radioprotection By Misoprostol (PGE$_1$ Methyl Analog) In Combination With Vitamin E, Selenomethionine and WR-3689794," *Eicosanoids and Other Bioactive Lipids in Cancer, Inflammation, and Radiation Injury 2*, edited by K. V. Honn et al., Plenum Press, New York, pp. 791-797, 1997.

EXAMINER	DATE CONSIDERED
	4/7/99

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

SIU 7356
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Kathleen C.M. Campbell — Art Unit:1614

Serial No.: 08/942,845 — Examiner:J.D. Goldberg

Filed: October 2, 1997

For: THERAPEUTIC USE OF D-METHIONINE TO REDUCE THE TOXICITY OF PLATINUM-CONTAINING ANTITUMOR COMPOUNDS

July 6, 1999

Preliminary Amendment

TO THE ASSISTANT COMMISSIONER FOR PATENTS,

SIR:

Prior to calculating the filing fee and prior to examination of the present application, please enter the following amendments and remarks.

In the Claims:

Please cancel claims 1-41 without prejudice or disclaimer of any of the subject matter contained therein.

Please enter the following new claims:

42. A method for preventing or reducing ototoxicity in a patient selected from the group consisting of a human, a cat, and a dog undergoing treatment with an anti-cancer

effective amount of a platinum-containing chemotherapeutic agent, comprising administering to said patient an anti-ototoxic effective amount of D-methionine.

2. A method for preventing or reducing weight loss in a patient selected from the group consisting of a human, a cat, and a dog undergoing treatment with an anti-cancer effective amount of a platinum-containing chemotherapeutic agent, comprising administering to said patient an anti-weight loss effective amount of D-methionine.

3. A method for preventing or reducing gastrointestinal toxicity in a patient selected from the group consisting of a human, a cat, and a dog undergoing treatment with an anti-cancer effective amount of a platinum-containing chemotherapeutic agent, comprising administering to said patient an anti-gastrointestinal toxicity effective amount of D-methionine.

4. A method for preventing or reducing neurotoxicity in a patient selected from the group consisting of a human, a cat, and a dog undergoing treatment with an anti-cancer effective amount of a platinum-containing chemotherapeutic agent, comprising administering to said patient an anti-neurotoxicity effective amount of D-methionine.

5. A method for preventing or reducing alopecia in a patient selected from the group consisting of a human, a cat, and a dog undergoing treatment with an anti-cancer effective amount of a platinum-containing chemotherapeutic agent, comprising administering to said patient an anti-alopecia effective amount of D-methionine.

6. The method of claim 1, wherein said D-methionine is administered prior to administration of said platinum-containing chemotherapeutic agent.

7. The method of claim 1, wherein said D-methionine is administered simultaneously with administration of said platinum-containing chemotherapeutic agent.

8. The method of claim 1, wherein said D-methionine is administered subsequently to administration of said platinum-containing chemotherapeutic agent.

9. The method of claim 1, wherein said effective amount of said D-methionine is administered to said patient in a time period from about 36 hours before administration of said platinum-containing chemotherapeutic agent to about 36 hours after administration of said platinum-containing chemotherapeutic agent.

10. The method of claim 1, wherein said effective amount of said D-methionine is administered to said patient in a time period from about 25 hours before administration of said platinum-containing chemotherapeutic agent to about 25 hours after administration of said platinum-containing chemotherapeutic agent.

11. The method of claim 1, wherein said effective amount of said D-methionine is administered to said patient in a time period from about 6 hours before administration of said platinum-containing chemotherapeutic agent to about 6 hours after administration of said platinum-containing chemotherapeutic agent.

12. The method of claim 1, wherein said effective amount of said D-methionine is administered to said patient in a time period from about 1 hour before administration of said platinum-containing chemotherapeutic agent to about 1 hour after administration of said platinum-containing chemotherapeutic agent.

13. The method of claim 1, wherein said effective amount of said D-methionine is administered to said patient in a time period from about one-half hour before

administration of said platinum-containing chemotherapeutic agent to about one-half hour after administration of said platinum-containing chemotherapeutic agent.

14. The method of claim 1, wherein said platinum-containing chemotherapeutic agent is selected from the group consisting of *cis*-diamminedi-chloroplatinum(II), *trans*-diaminidichloroplatinum(II), *cis*-diammine-diaquaplatinum(II)-ion, chloro(diethyl-enetriamine)-platinum(II) chloride, dichloro(ethylene-diamine)-platinum(II), diammine(1,1-cyclobutanedi-carboxylato)-platinum(II), spiroplatin, dichlorotrans-dihydroxybisisopropolamine platinum IV (iproplatin), diammine(2-ethylmalonato)-platinum(II), ethylenediamine-malonatoplatinum(II), aqua(1,2-diaminodyclohexane)-sulfatoplatinum(II), (1,2-diaminocyclohexane)malonato-platinum(II), (4-carboxy-phthalato)(1,2-diaminocyclo-hexane)-platinum(II), (1,2-diaminocyclohexane)-(isocitrato)platinum(II), (1,2-diaminocyclohexane)-*cis*(pyruvato)platinum(II), and (1,2-diaminocyclohexane)-oxalatoplatinum(II).

15. The method of claim 14, wherein said platinum-containing chemotherapeutic agent is *cis*-diamminedichloro-platinum(II).

16. The method of claim 1, wherein said effective amount of D-methionine is in the range of from about 0.1 mg/kg body weight to about 500 mg/kg body weight.

17. The method of claim 1, wherein said effective amount of D-methionine is in the range of from about 1 mg/kg body weight to about 400 mg/kg body weight.

18. The method of claim 1, wherein said effective amount of D-methionine is in the range of from about 10 mg/kg body weight to about 300 mg/kg body weight.

19. The method of claim 1, wherein said effective amount of D-methionine is in the range of from about 1 mg/kg body weight to about 100 mg/kg body weight.

20. The method of claim 1, wherein said effective amount of D-methionine is in the range of from about 10 mg/kg body weight to about 75 mg/kg body weight.

21. The method of claim 1, wherein said effective amount of D-methionine in relation to said anti-cancer effective amount of said platinum-containing chemotherapeutic agent is in the range of from about 4:1 to about 167:1, D-methionine:platinum-containing chemotherapeutic agent, on a molar basis.

22. The method of claim 1, wherein said effective amount of D-methionine in relation to said anti-cancer effective amount of said platinum-containing chemotherapeutic agent is in the range of from about 4.25:1 to about 100:1, D-methionine:platinum-containing chemotherapeutic agent, on a molar basis.

23. The method of claim 1, wherein said effective amount of D-methionine in relation to said anti-cancer effective amount of said platinum-containing chemotherapeutic agent is in the range of from about 4.68:1 to about 20:1, D-methionine:platinum-containing chemotherapeutic agent, on a molar basis.

24. The method of claim 1, wherein said effective amount of D-methionine in relation to said anti-cancer effective amount of said platinum-containing chemotherapeutic agent is about 18.75:1, D-methionine:platinum-containing chemotherapeutic agent, on a molar basis.

25. The method of claim 1, wherein said D-methionine is administered orally or parenterally.

26. The method of claim 25, wherein said platinum-containing chemotherapeutic agent is administered parenterally.

27. The method of claim 26, wherein said parenteral administration is by slow intravenous infusion.

28. The method of claim 1, further comprising administering to said patient a supplemental amount of D-methionine in the range of from about 0.1 mg/kg body weight to about 500 mg/kg body weight per week during and/or after the course of treatment with said platinum-containing chemotherapeutic agent.

29. The method of claim 28, wherein said supplemental amount of D-methionine is administered orally or parenterally.

30. A method for preventing or reducing ototoxicity in a patient undergoing treatment with an anti-cancer effective amount of a platinum-containing chemotherapeutic agent selected from the group consisting of cisplatin, carboplatin, and iproplatin, comprising:

intravenously administering to said patient about 10 mg/kg body weight to about 75 mg/kg body weight of D-methionine, or a pharmaceutically acceptable salt thereof, or

D-methionine or a pharmaceutically acceptable salt thereof in a molar ratio of about 18.75:1, D-methionine:platinum-containing chemotherapeutic agent,

within about one-half hour before administration of said platinum-containing chemotherapeutic agent to about one-half hour after administration of said platinum-containing chemotherapeutic agent.

31. The method of claim 1, wherein said platinum-containing chemotherapeutic agent is cisplatin.

32. The method of claim 2, wherein said platinum-containing chemotherapeutic agent is cisplatin.

33. The method of claim 3, wherein said platinum-containing chemotherapeutic agent is cisplatin.

34. The method of claim 4, wherein said platinum-containing chemotherapeutic agent is cisplatin.

35. The method of claim 5, wherein said platinum-containing chemotherapeutic agent is cisplatin.

36. A method for preventing or reducing ototoxicity in a patient selected from the group consisting of a human, a cat, and a dog undergoing treatment with an anti-cancer effective amount of a platinum-containing chemotherapeutic agent, comprising administering to said patient an anti-ototoxic effective amount of D,L-methionine.

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UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

KD

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
08/942,845	10/02/97	CAMPBELL	K	SIU7356

000321 HM12/0806
SENNIGER POWERS LEAVITT AND ROEDEL
ONE METROPOLITAN SQUARE
16TH FLOOR
ST LOUIS MO 63102

EXAMINER	
GOLDBERG, J	
ART UNIT	**PAPER NUMBER**
1614	17

DATE MAILED: 08/06/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

0

Office Action Summary	Application No. 08/942,845	Applicant(s) Campbell
	Examiner Jerome D. Goldberg	Group Art Unit 1614

☒ Responsive to communication(s) filed on *Jul 6, 1999*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *42-77* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *42-77* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

The request filed on July 06, 1997 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/942,845 is acceptable and a CPA has been established. An action on the CPA follows.

Applicant elected the specific entranced combination of cisplatin and D-mentionine with traversed in Paper No. 5. This restriction requirement was modified (Paper No. 6) in that the D and D, L methionine will be examined with the cisplatin.

The claims are being examined as they read on the elected enhanced combination of cisplatin and methionine.

Claims 1-36 have been renumbered as claims 42-77.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 42-77 are rejected under 35 U.S.C. 103(a) as being unpatentable over the Newman et al. reference of record.

The Newman et al. reference teaches cisplatin at 16 mg/kg with methionine being administered 15 minutes before or one hour after the cisplatin with a "decrease... the toxicity of the pT compd." (last two lines), the reference does not teach the specific toxicities involved. In view of this, one skilled in the art would be motivated to employ methionine to reduce toxic

effect of cisplatin. Clearly, the specific toxic effects being claimed would be reduced by employing methionine.

Claims 42-54, 57-70 and 77 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the specific platinum-containing chemotherapeutic agent disclosed, does not reasonably provide enablement for the term "Platinum-containing chemotherapeutic agent". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The term "platinum-containing chemotherapeutic agent" in claims 42-54, 57-70, and 77 lacks clear exemplary support in the specification as filed.

Claims 42-77 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the specific cancers disclosed, does not reasonably provide enablement for the term "anti-cancer". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The term "anti-cancer" in claims 42-77 lacks clear exemplary support in the specification as filed.

The cancer therapy art remains highly unpredictable, and no example exists for of a efficacy single product against cancer generally. Therefore, based on the unpredictable nature of the invention and state of the prior art, the lack of guidance and working example, and the

extreme breadth of the claims, one skilled in this art could not use the entire scope of the claimed invention without undue experimentation.

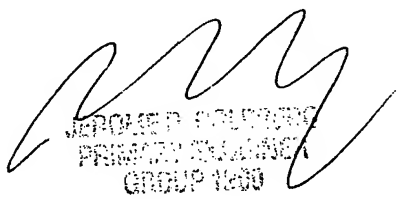
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner J. D. Goldberg, whose telephone number is (703) 308-4606. The examiner can normally be reached on Monday through Thursday from 9:00 a.m. to 3:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Cintins, can be reached on (703) 308-4725. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556 or 305-3592.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

J. Goldberg:jmr

July 23, 1999



OPEN HOUSE PROGRAM

BIO

Technology Center 1600/2900 & SIPA
August 24-25, 1999

Location: Crystal [illegible]
1999 Jefferson Davis Highway
Arlington, VA 22202

Time: August 24 - registration at 8, program begins at 8:30
August 25 - program begins at 8

Cost: $70 (Includes: program, lunch on 8/24, reception on 8/24)

Program Includes:

- Patent Operations Issues
- Quality Update
- Biotech Policy
- PTO Strategic Planning
- Patent Automation Initiatives
- Town Hall Meeting
- Luncheon Speech by Q. Todd Dickinson *Acting Commissioner of Patents and Trademarks*
- Appeals and Interferences
- Design Issues
- Tours of the Technology Center
- Demonstrations of Automation Tools *Including PatentIn*
- Panels of SPEs on current topics

For more information or to register by phone, call 703-308-1234; your payment can be made by credit card or check made payable to "BIO"

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of Kathleen C. M. Campbell Art Unit 1614
Continued Prosecution Application
Serial No. 08/942,845
Filed October 2, 1997
For THERAPEUTIC USE OF D-METHIONINE TO REDUCE THE TOXICITY OF PLATINUM-CONTAINING ANTI-TUMOR COMPOUNDS
Examiner: J.D. Goldberg

February 4, 2000

AMENDMENT D

TO THE ASSISTANT COMMISSIONER FOR PATENTS,

SIR:

In response to the Office action of August 6, 1999, the time for response to which is extended to February 4, 2000, under 37 C.F.R. §1.136(a), please enter the following amendments to the above referenced application:

IN THE CLAIMS:

Please amend claims 42-56, 62-65, 67, 69 and 71-77 as follows:

42. (amended) A method for preventing or reducing ototoxicity in a patient selected from the group consisting of a human, a cat, and a dog undergoing treatment with a[n anti-cancer] chemotherapeutic effective amount of [a platinum-containing chemotherapeutic agent] an anti-tumor platinum-coordination compound, comprising administering to said patient an anti-ototoxic effective amount of D-methionine.

43. (amended) A method for preventing or reducing weight loss in a patient selected from the group consisting of a human, a cat, and a dog undergoing treatment with a[n anti-cancer] chemotherapeutic effective amount of [a platinum-containing chemotherapeutic agent] an anti-tumor platinum-coordination compound, comprising administering to said patient an anti-weight loss effective amount of D-methionine.

44. (amended) A method for preventing or reducing gastrointestinal toxicity in a patient selected from the group consisting of a human, a cat, and a dog undergoing

treatment with a[n anti-cancer] chemotherapeutic effective amount of [a platinum-containing chemotherapeutic agent] an anti-tumor platinum-coordination compound, comprising administering to said patient an anti-gastrointestinal toxicity effective amount of D-methionine.

45. (amended) A method for preventing or reducing neurotoxicity in a patient selected from the group consisting of a human, a cat, and a dog undergoing treatment with a[n anti-cancer] chemotherapeutic effective amount of [a platinum-containing chemotherapeutic agent] an anti-tumor platinum-coordination compound, comprising administering to said patient an anti-neurotoxicity effective amount of D-methionine.

46. (amended) A method for preventing or reducing alopecia in a patient selected from the group consisting of a human, a cat, and a dog undergoing treatment with a[n anti-cancer] chemotherapeutic effective amount of [a platinum-containing chemotherapeutic agent] an anti-tumor platinum-coordination compound, comprising administering to said patient an anti-alopecia effective amount of D-methionine.

Claim 47, line 2, replace "platinum-containing chemotherapeutic agent" with -- anti-tumor platinum-coordination compound--.

Claim 48, line 2, replace "platinum-containing chemotherapeutic agent" with -- anti-tumor platinum-coordination compound--.

Claim 49, line 2, replace "platinum-containing chemotherapeutic agent" with -- anti-tumor platinum-coordination compound--.

50. (amended) The method of claim 42, wherein said effective amount of said D-methionine is administered to said patient in a time period from about 36 hours before administration of said [platinum-containing chemotherapeutic agent] anti-tumor platinum-coordination compound to about 36 hours after administration of said [platinum-containing chemotherapeutic agent] anti-tumor platinum-coordination compound.

51. (amended) The method of claim 42, wherein said effective amount of said D-methionine is administered to said patient in a time period from about 25 hours before

administration of said [platinum-containing chemotherapeutic agent] anti-tumor platinum-coordination compound to about 25 hours after administration of said [platinum-containing chemotherapeutic agent] anti-tumor platinum-coordination compound.

52. (amended) The method of claim 42, wherein said effective amount of said D-methionine is administered to said patient in a time period from about 6 hours before administration of said [platinum-containing chemotherapeutic agent] anti-tumor platinum-coordination compound to about 6 hours after administration of said [platinum-containing chemotherapeutic agent] anti-tumor platinum-coordination compound.

53. (amended) The method of claim 42, wherein said effective amount of said D-methionine is administered to said patient in a time period from about 1 hour before administration of said [platinum-containing chemotherapeutic agent] anti-tumor platinum-coordination compound to about 1 hour after administration of said [platinum-containing chemotherapeutic agent] anti-tumor platinum-coordination compound.

54. (amended) The method of claim 42, wherein said effective amount of said D-methionine is administered to said patient in a time period from about one-half hour before administration of said [platinum-containing chemotherapeutic agent] anti-tumor platinum-coordination compound to about one-half hour after administration of said [platinum-containing chemotherapeutic agent] anti-tumor platinum-coordination compound.

Claim 55, lines 1-2, replace "platinum-containing chemotherapeutic agent" with -- anti-tumor platinum-coordination compound--.

Claim 56, lines 1-2, replace "platinum-containing chemotherapeutic agent" with -- anti-tumor platinum-coordination compound--.

62. (amended) The method of claim 42, wherein said effective amount of D-methionine in relation to said [anti-cancer] chemotherapeutic effective amount of said [platinum-containing chemotherapeutic agent] anti-tumor platinum-coordination compound is in the range of from about 4:1 to about 167:1, D-methionine:[platinum-

containing chemotherapeutic agent] anti-tumor platinum-coordination compound, on a molar basis.

63. (amended) The method of claim 42, wherein said effective amount of D-methionine in relation to said [anti-cancer] chemotherapeutic effective amount of said [platinum-containing chemotherapeutic agent] anti-tumor platinum-coordination compound is in the range of from about 4.25:1 to about 100:1, D-methionine:[platinum-containing chemotherapeutic agent] anti-tumor platinum-coordination compound, on a molar basis.

64. (amended) The method of claim 42, wherein said effective amount of D-methionine in relation to said [anti-cancer] chemotherapeutic effective amount of said [platinum-containing chemotherapeutic agent] anti-tumor platinum-coordination compound is in the range of from about 4.68:1 to about 20:1, D-methionine:[platinum-containing chemotherapeutic agent] anti-tumor platinum-coordination compound, on a molar basis.

65. (amended) The method of claim 42, wherein said effective amount of D-methionine in relation to said [anti-cancer] chemotherapeutic effective amount of said [platinum-containing chemotherapeutic agent] anti-tumor platinum-coordination compound is about 18.75:1, D-methionine:[platinum-containing chemotherapeutic agent] anti-tumor platinum-coordination compound, on a molar basis.

Claim 67, lines 1-2, replace "platinum-containing chemotherapeutic agent" with --anti-tumor platinum-coordination compound--.

Claim 69, line 4, replace "platinum-containing chemotherapeutic agent" with --anti-tumor platinum-coordination compound--.

71. (amended) A method for preventing or reducing ototoxicity in a patient undergoing treatment with a[n anti-cancer] chemotherapeutic effective amount of [a platinum-containing chemotherapeutic agent] an anti-tumor platinum-coordination compound selected from the group consisting of cisplatin, carboplatin, and iproplatin, comprising:

intravenously administering to said patient about 10 mg/kg body weight to about 75 mg/kg body weight of D-methionine, or a pharmaceutically acceptable salt thereof, or

D-methionine or a pharmaceutically acceptable salt thereof in a molar ratio of about 18.75:1, D-methionine:[platinum-containing chemotherapeutic agent] anti-tumor platinum-coordination compound,

within about one-half hour before administration of said [platinum-containing chemotherapeutic agent] anti-tumor platinum-coordination compound to about one-half hour after administration of said [platinum-containing chemotherapeutic agent] anti-tumor platinum-coordination compound.

Claim 72, lines 1-2, replace "platinum-containing chemotherapeutic agent" with -- anti-tumor platinum-coordination compound--.

Claim 73, lines 1-2, replace "platinum-containing chemotherapeutic agent" with -- anti-tumor platinum-coordination compound--.

Claim 74, lines 1-2, replace "platinum-containing chemotherapeutic agent" with -- anti-tumor platinum-coordination compound--.

Claim 75, lines 1-2, replace "platinum-containing chemotherapeutic agent" with -- anti-tumor platinum-coordination compound--.

Claim 76, lines 1-2, replace "platinum-containing chemotherapeutic agent" with -- anti-tumor platinum-coordination compound--.

77. (amended) [A] The method of claim 42, wherein [for preventing or reducing ototoxicity in a patient selected from the group consisting of a human, a cat, and a dog undergoing treatment with an anti-cancer effective amount of a platinum-containing chemotherapeutic agent, comprising administering to said patient] an anti-ototoxic effective amount of D,L-methionine is administered to said patient.

Please add the following new claim 78:

78. The method of claim 42, wherein an anti-ototoxic effective amount of a methionine protective agent consisting essentially of D-methionine is administered to said patient.

REMARKS

Reconsideration of the application claims as amended and in view of the following remarks is respectfully requested.

Non-Obviousness

Claims 42-77 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over the Newman et al. reference. In light of the declaration of Dr. Kathleen C.M. Campbell submitted herewith and the remarks presented hereunder, it is respectfully submitted that claims 42-77 define patentably over the cited reference.

The present invention is directed to the therapeutic use of D-methionine to prevent ototoxicity, weight loss, gastrointestinal toxicity, neurotoxicity and alopecia in a human, cat or a dog undergoing treatment with a chemotherapeutic effective amount of an anti-tumor platinum-coordination compound. As set forth in detail in Dr. Campbell's declaration, Newman et al. cannot be said to provide the necessary teaching, suggestion, motivation, or reasonable expectation of success required to lead one ordinarily skilled in the art to the subject matter of the present invention.

The Newman reference only describes the administration of thiourea and L-methionine in combination with cisplatin to mice inoculated with leukemia cells, presumably for the prevention of nephrotoxicity (kidney damage). Newman conveys no teaching or suggestion of any method for inhibiting ototoxicity, weight loss, gastrointestinal toxicity, neurotoxicity or alopecia. In fact, Newman fails to specify any particular form of toxicity.

As explained in the attached declaration of Dr. Campbell, one skilled in the art would most likely presume that the toxic effect observed by Newman was nephrotoxicity. However, one ordinarily skilled in the art would not interpret the reference as teaching or suggesting that the combination of L-methionine and cisplatin was necessarily successful in reducing nephrotoxicity. The Newman reference does not include any substantive data concerning the administration of L-methionine in reducing or protecting against nephrotoxicity in mice and the

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NOTICE OF ALLOWANCE AND ISSUE FEE DUE

APPLICATION NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT	DATE MAILED
First Named Applicant				

TITLE OF INVENTION

ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED.

THE ISSUE FEE MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED.

HOW TO RESPOND TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.
If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is changed, pay twice the amount of the FEE DUE shown above and notify the Patent and Trademark Office of the change in status, or

B. If the status is the same, pay the FEE DUE shown above.

If the SMALL ENTITY is shown as NO:

A. Pay FEE DUE shown above, or

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II. Part B-Issue Fee Transmittal should be completed and returned to the Patent and Trademark Office (PTO) with your ISSUE FEE. Even if the ISSUE FEE has already been paid by charge to deposit account, Part B Issue Fee Transmittal should be completed and returned. If you are charging the ISSUE FEE to your deposit account, section "4b" of Part B-Issue Fee Transmittal should be completed and an extra copy of the form should be submitted.

III. All communications regarding this application must give application number and batch number.
Please direct all communications prior to issuance to Box ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

YOUR COPY

Notice of Allowability

Application No.	Applicant(s)
08/942,845	Campbell
Examiner	**Group Art Unit**
Jerome D. Goldberg	1614

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance and Issue Fee Due or other appropriate communication will be mailed in due course.

☒ This communication is responsive to *02/09/2000*.

☒ The allowed claim(s) is/are *42-76 and 78*.

☐ The drawings filed on _____ are acceptable.

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

A SHORTENED STATUTORY PERIOD FOR RESPONSE to comply with the requirements noted below is set to EXPIRE **THREE MONTHS** FROM THE "DATE MAILED" of this Office action. Failure to timely comply will result in ABANDONMENT of this application. Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

☐ Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL APPLICATION, PTO-152, which discloses that the oath or declaration is deficient. A SUBSTITUTE OATH OR DECLARATION IS REQUIRED.

☒ Applicant MUST submit NEW FORMAL DRAWINGS

☐ because the originally filed drawings were declared by applicant to be informal.

☐ including changes required by the Notice of Draftsperson's Patent Drawing Review, PTO-948, attached hereto or to Paper No. _____.

☐ including changes required by the proposed drawing correction filed on _____, which has been approved by the examiner.

☐ including changes required by the attached Examiner's Amendment/Comment.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the reverse side of the drawings. The drawings should be filed as a separate paper with a transmittal lettter addressed to the Official Draftsperson.

☐ Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Any response to this letter should include, in the upper right hand corner, the APPLICATION NUMBER (SERIES CODE/SERIAL NUMBER). If applicant has received a Notice of Allowance and Issue Fee Due, the ISSUE BATCH NUMBER and DATE of the NOTICE OF ALLOWANCE should also be included.

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

☒ Interview Summary, PTO-413

☒ Examiner's Amendment/Comment

☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material

☐ Examiner's Statement of Reasons for Allowance

1. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Mr. John K. Roedel, Jr. on May 1, 2000.

2. The application has been amended as follows: The term ", wherein the D-methionine is substantially free of the L-isomer" has been added to the end of claims 42-46 and 71. Claim 77 has been canceled, without prejudice. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jerome D. Goldberg whose telephone number is (703) 308-4606.

JDG

May 1, 2000

Interview Summary

Application No.	Applicant(s)
08/942,845	Campbell
Examiner	**Group Art Unit**
Jerome D. Goldberg	1614

All participants (applicant, applicant's representative, PTO personnel):

(1) *Jerome D. Goldberg* (3) _____

(2) *Mr. John K. Roedel, Jr.* (4) _____

Date of Interview *May 1, 2000*

Type: ☒ Telephonic ☐ Personal (copy is given to ☐ applicant ☐ applicant's representative).

Exhibit shown or demonstration conducted: ☐ Yes ☒ No. If yes, brief description:

Agreement ☒ was reached. ☐ was not reached.

Claim(s) discussed: *42-46 and 77*

Identification of prior art discussed:

Description of the general nature of what was agreed to if an agreement was reached, or any other comments:
Ok to add the term ", wherein the D-methionine is substantially free of the L-isomer" to the end of claims 42-46 and 71.
Ok to cancel claim 77, without prejudice.

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendents which would render the claims allowable is available, a summary thereof must be attached.)

1. ☒ It is not necessary for applicant to provide a separate record of the substance of the interview.

Unless the paragraph above has been checked to indicate to the contrary, A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a response to the last Office action has already been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW.

2. ☐ Since the Examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action. Applicant is not relieved from providing a separate record of the interview unless box 1 above is also checked.

Examiner Note: You must sign and stamp this form unless it is an attachment to a signed Office action.

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